

**Incidentally discovered adrenal tumours,  
adrenal metastases, and  
pheochromocytomas**  
Clinical and epidemiological aspects

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Gothenburg, Sweden

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UNIVERSITY OF GOTHENBURG

**Incidentally discovered adrenal tumours, adrenal metastases, and pheochromocytomas –  
Clinical and epidemiological aspects**

A doctoral thesis at a University in Sweden is produced either as a monograph or as a collection of papers. In the latter case, the introductory part constitutes the formal thesis, which summarises the accompanying papers.

**Front cover:** The first depiction of the adrenal glands by Italian anatomist B. Eustachius, detail. Originally published in the *Opuscula Anatomica*, Venice 1563/64, here reprinted from the *Tabula anatomicae*, Rome 1728. Wellcome Trust Library, London, UK.

**Facing page (bottom):** Excerpt from the poem *Verschenkter Rat* by Ilse Aichinger (2).

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Research, like any creative activity, requires a  
firm belief in the future

*To Klara and Astrid*

Dein erstes Schachbuch,  
Ibsens Briefe,  
nimms hin,  
wenn du kannst,  
da, nimm schon  
oder willst du lieber  
die Blattkehrer  
von deiner Wiese treiben  
und Ibsens Ziegen  
darauf,  
gleich weiß, gleich glänzend?  
Es gibt Ziegen und es gibt Ibsens Ziegen,  
Es gibt den Himmel und es gibt eine  
spanische Eröffnung.  
Hör gut hin, Kleiner,  
Es gibt Weißblech, sagen sie,  
es gibt die Welt,  
prüfe, ob sie nicht lügen.





## Abstract

### Incidentally discovered adrenal tumours, adrenal metastases, and pheochromocytomas – Clinical and epidemiological aspects

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With increasing use of high resolution radiological imaging incidentally discovered adrenal tumours (adrenal incidentalomas, AI) have become a common clinical problem. The aim of work-up and follow-up of patients with AI is to detect malignant (primary or metastatic) and/or hormone-producing tumours. The frequency of AI, and the clinical and patient reported outcomes of a two-year follow-up programme for AI was investigated in an unselected population undergoing radiology at all departments of radiology in Western Sweden during 18 months. The results of surgery for adrenal metastasis, and the impact of background variables on survival was analysed in a consecutive series of patients treated at the Sahlgrenska University Hospital (1996-2007). Pheochromocytomas (Pheo) and paragangliomas (PGL) are rare catecholamine-producing tumours originating from the adrenal medulla and sympathetic and parasympathetic ganglia that may be detected as AI. The frequency of germ-line mutations (in the *RET*-, *SDHB*-, *SDHC*-, *SDHD*- and *VHL*-genes) was studied in all living patients with Pheo and abdominal PGL with apparently sporadic presentation registered in the National Cancer Register for Western Sweden 1958-2009.

At focused evaluation of abdominal computed tomography the frequency of AI was 4.5 %. In patients with AI (without extra-adrenal malignancy) 6.6 % were operated on suspicion of malignant or hormone-producing tumours; hormone-producing tumours were verified in 3.1 %. No primary adrenal malignancy was found. All patients with hormone-producing or malignant tumours were identified at first evaluation. Further follow-up had low impact on Health-Related Quality of Life, but did not confer any benefit. Surgery for adrenal metastasis was associated with low perioperative morbidity and mortality. Factors associated with prolonged survival were potentially curative surgery, tumour type, no previous surgery for metastases, and long disease-free interval. It should be considered for all patients with isolated adrenal metastasis, and may be part of the multi-modal treatment in disseminated disease. Germ-line mutations were found in 5.6 % of patients with apparently sporadic Pheo/abdominal PGL, which was fewer than in other published series. All mutations were seen in *SDHB* and *RET*. Notably, no patient with *SDHB*-mutation has evidence of malignant disease after 16-28 years follow-up, even though this genotype has been associated with a high rate of malignancy.

**Keywords:** Incidental Findings; Adrenal incidentaloma; Adrenal Gland Neoplasms; Adrenalectomy; Follow-Up Studies; Quality of Life; Pheochromocytoma/epidemiology; Pheochromocytoma/genetics; Paraganglioma/epidemiology; Paraganglioma/genetics

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## List of papers

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

- I. Lilian Hammarstedt, Andreas Muth, Bo Wängberg, Lena Björnelid, Helga A. Sigurjónsdóttir, Galina Götherström, Erik Almqvist, Håkan Widell, Sture Carlsson, Stefan Ander & Mikael Hellström: Adrenal lesion frequency: A prospective, cross-sectional CT study in a defined region, including systematic re-evaluation. *Acta Radiologica*, 2010 Dec; 51(10): 1149-56.
- II. Andreas Muth, Lilian Hammarstedt, Mikael Hellström, Helga A. Sigurjónsdóttir, Erik Almqvist & Bo Wängberg: Cohort study with two-year follow-up of incidentally discovered adrenal lesions in an unselected population undergoing radiological examinations. *British Journal of Surgery*, in press.
- III. Andreas Muth, Charles Taft, Lilian Hammarstedt, Lena Björnelid, Mikael Hellström & Bo Wängberg: Patient reported impacts of a conservative management programme for the clinically inapparent adrenal mass. Submitted.
- IV. Andreas Muth, Fredrik Persson, Svante Jansson, Viktor Johanson, Håkan Ahlman & Bo Wängberg: Prognostic factors for survival after surgery for adrenal metastasis. *European Journal of Surgical Oncology*, 2010 Jul; 36(7): 699-704.
- V. Andreas Muth, Frida Abel, Svante Jansson, Ola Nilsson, Håkan Ahlman & Bo Wängberg: Prevalence of germ-line mutations in patients with pheochromocytoma or abdominal paraganglioma and sporadic presentation: a population-based study in western Sweden. Manuscript.

## Abbreviations

1 mg-DST	1 mg overnight dexamethasone suppression test
A	adrenaline
ACC	adrenocortical carcinoma
AI	adrenal incidentaloma(s)
AIQ	Adrenal Incidentaloma Impact Questionnaire
ARR	aldosterone renin ratio
CA	catecholamine(s)
COMT	catechol-O-methyltransferase
CT	computed tomography
DFI	disease-free interval
DHEA	dehydroepiandrosterone
HADS	Hospital Anxiety and Depression Scale
HPA	hypothalamic-pituitary-adrenal
HRQoL	Health-Related Quality of Life
HU	Hounsfield Units
MEN2	multiple endocrine neoplasia type 2
MIBG	meta-iodo-benzyl-guanidine
MLPA	Multiplex Ligation-dependent Probe Amplification
MRI	magnetic resonance imaging
NA	noradrenaline
NCR	National Cancer Register
NF1	neurofibromatosis type 1
NIH	United States National Institute of Health
PA	primary aldosteronism
PET	positron-emission tomography
PGL	paraganglioma(s)
Pheo	pheochromocytoma(s)
RET	rearranged during transfection
SDH	succinate dehydrogenase
SF-36	Short Form-36
SH	subclinical hypercortisolism
Sv	Sievert
VHL	von Hippel-Lindau
VMA	vanillylmandelic acid

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## Introduction

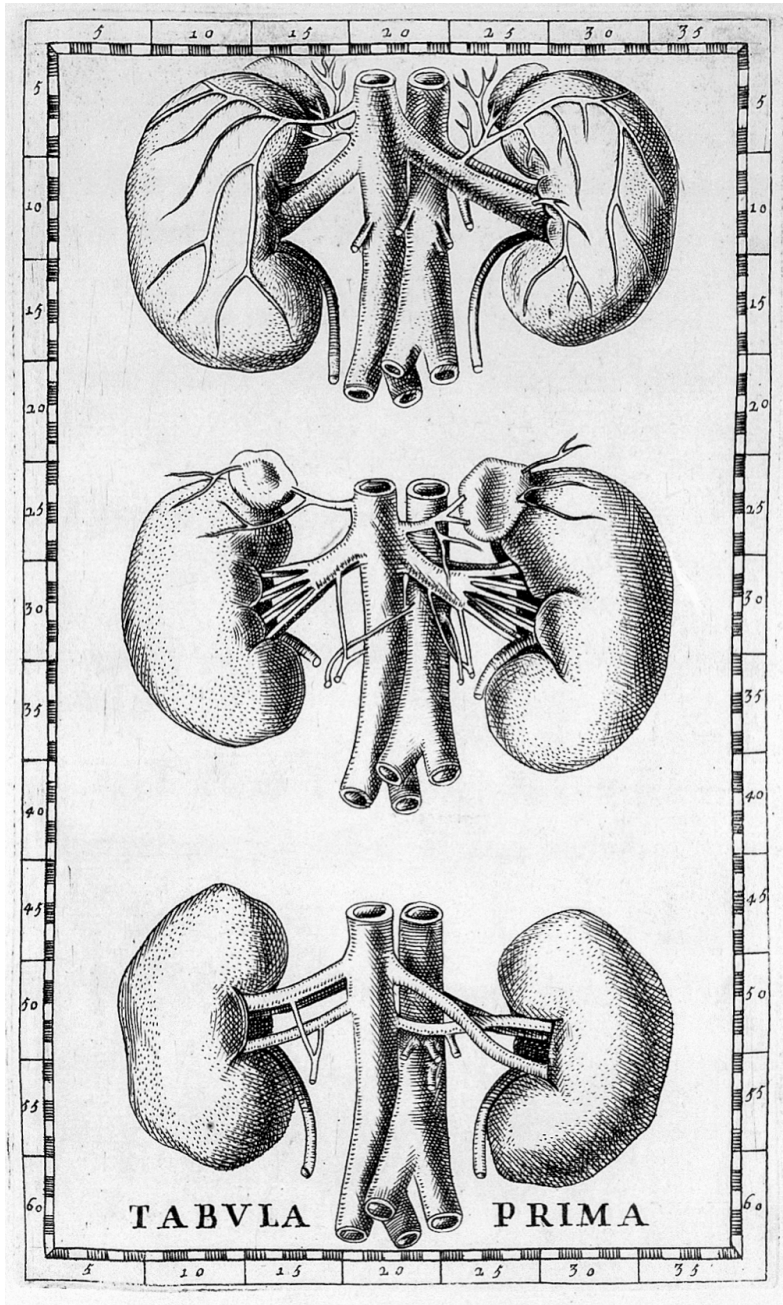
### *The adrenal glands*

The adrenal glands are endocrine organs situated in the retroperitoneum. The Italian anatomist Bartolomaeus Eustachius (Figure 1) first described the adrenal glands in the "*Opuscula Anatomica*" (6) (Figure 2), published in 1563/64. Their critical importance for maintaining body homeostasis was first clinically appreciated by Addison, who published his observations "*On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules*" in 1855 (7). Experimental support of Addison's observations was provided the following year by Brown-Séquard, in a series of animal experiments with uni- or bilateral adrenalectomies (8). In 1895 Oliver and Schäfer (9) demonstrated pressor effects of injected extracts of the adrenal medulla, and, in 1904, adrenaline was synthesised by Stolz (10). During the first part of the 20<sup>th</sup> century the adrenocortical hormones were isolated, and in 1949 Hench et al. (11) reported on the therapeutic effects of Compound E (today known as cortisone) on rheumatoid arthritis. In 1950 Kendall, Reichstein and Hench were awarded the Nobel Prize "for their discoveries relating to hormones of the adrenal cortex, their structure and biological effects" (12).



**Figure 1.** *B. Eustachius (1520- 1574) (1). Wellcome Trust Library, London, UK.*

On axial imaging the adrenal glands anteriorly have a body and posteriorly a medial and a lateral limb. The size of the normal adrenal gland increases with age (13), and may increase in conditions such as depression (14, 15). The mean weight of an adult adrenal gland removed at surgery is 4-5 g (6 g at autopsy) (16, 17). Embryologically and functionally, the adrenal glands have two parts, the cortex derived from the mesoderm, and the medulla of neuro-ectodermal origin. The adrenal cortex is subdivided in three layers: the thin outer zona glomerulosa, the middle lipid-rich zona fasciculata, and the inner pigment-rich zona reticularis (16). The proliferative zone between fasciculata and reticularis is sometimes referred to as zona intermedia. The zona glomerulosa secretes mineralocorticoids, *e.g.* aldosterone, while the zona fasciculata and the zona reticularis secrete cortisol and androgens, *e.g.* dehydroepiandrosterone (DHEA). The sulfotransferase responsible for synthesis of DHEA-sulphate is mainly located in the zona reticularis. The adrenal medulla can be regarded as a collection of modified postsynaptic sympathetic neurons without axons, which synthesise, store, and secrete catecholamines (CA) directly into the bloodstream, in contrast to other postganglionic sympathetic neurons, which exert their effects by direct synaptic transmission to the effector organs.



**Figure 2.** Anatomical plate originally published in the *Opuscula anatomica*, Venice 1563/64. Reproduced in the *Tabulae anatomicae*, Rome, 1728 (18). Wellcome Trust Library, London, UK.



### **Biological function of corticosteroids**

The corticosteroids are synthesised from cholesterol. The most important steroids synthesised in the adrenal cortex are cortisol and aldosterone.

#### *Cortisol*

Cortisol is secreted under direct control of the anterior pituitary gland via the adrenocorticotrophic hormone (ACTH). Cortisol mobilises readily available energy in the body by stimulating lipolysis, inhibiting protein synthesis, and facilitating amino acid mobilisation from extra-hepatic sources, decreasing cell glucose utilisation, and stimulating gluconeogenesis. Cortisol acts in concert with catecholamines to maintain vascular tone and endothelial integrity. Cortisol also has potent anti-inflammatory effects (19).

#### *Aldosterone*

Aldosterone forms part of the renin-angiotensin-aldosterone system, which maintains blood pressure and renal perfusion pressure. Aldosterone acts through up-regulation of the apical epithelial Na<sup>+</sup> channels and the basal Na<sup>+</sup>/K<sup>+</sup>-ATPase in the renal cortical collecting duct cells, with a net effect of Na<sup>+</sup> and water retention and increased urinary K<sup>+</sup> excretion (20).

### **Metabolism and biological function of catecholamines**

The adrenal medulla secretes adrenaline (A) and noradrenaline (NA), both derivatives of the amino acid tyrosine. A and NA are inactivated by methylation catalysed by the enzyme catechol-O-methyltransferase (COMT). The resulting metanephrines rapidly undergo sulphate conjugation, or further degradation by reduction or oxidation. All CA and their metabolites are present in urine, but the quantitatively dominating substances are vanillylmandelic acid (VMA), conjugated metanephrines and homovanillic acid (21). In CA-secreting tumours the release of A and/or NA may occur intermittently, however, the degradation of CA to metanephrines by COMT occurs constantly in the tumour, and the plasma levels of metanephrines show a direct correlation with tumour size (22). Approximately 80 % of the secretion from the medulla is A and 20 % NA.

CA effects are mediated by  $\alpha$ - and  $\beta$ -adrenoceptors on the effector organs. Adrenoceptors can be divided into several receptor subtypes. A excites both  $\alpha$ - and  $\beta$ -adrenoceptors approximately equally, while NA mainly excites  $\alpha$ -adrenoceptors.  $\alpha$ -adrenoceptor mediated effects include peripheral vasoconstriction, pupil dilatation, intestinal relaxation, intestinal and bladder sphincter contraction, and pilomotor contraction.  $\beta_1$ -adrenoceptors mediate increased heart rate and heart muscle contractility, while  $\beta_2$ -adrenoceptors mediate bronchodilatation and metabolic effects, *e.g.* increased glycolysis and lipolysis. Increased heart rate and contractility, together with peripheral vasoconstriction leads to an increased systemic blood pressure (19).

## ***Tumours of the adult adrenal glands***

Primary adrenal tumours often present with specific symptoms related to unregulated secretion of hormones, non-specific symptoms due to the local mass, and/or to the extent of tumour burden and metastatic disease.

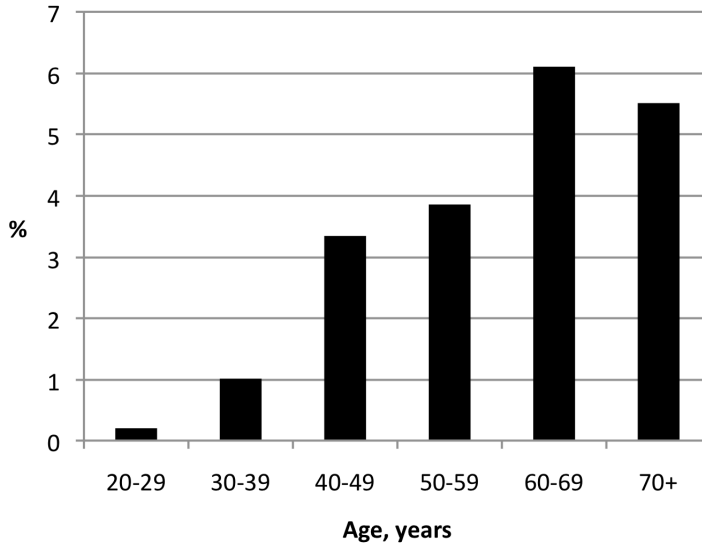
### **Tumours of the adrenal cortex**

#### *Adrenocortical adenoma*

In autopsy series adrenal adenomas have been reported in 1.4 – 8.7 % (23-29), increasing with age (Figure 3). Most adenomas are non-functioning (30). Cortisol-producing tumours present with signs and symptoms of hypercortisolism, first described by Cushing in 1912 (31). Common signs and symptoms include easy bruising, facial plethora, proximal muscle weakness, dorsocervical fat pads (“buffalo hump”), and central obesity, and fatigue. Hypertension, depression, diabetes type 2, and vertebral osteoporosis can be associated with hypercortisolism. Due to a significant overlap with other conditions no single sign, or combination of signs and symptoms is diagnostic of hypercortisolism (32). Aldosteronomas are benign, aldosterone-secreting tumours, usually < 20 mm in diameter. Clinically they present with primary aldosteronism (PA), a syndrome characterised by hypertension and often hypokalemia, first described by Conn in 1955 (33). PA is one of the most common forms of secondary hypertension; in a study of hypertensive patients from two primary care catchment areas in southern Sweden, the prevalence of PA was 8.5 % (34). In aldosterone-producing adenomas and hereditary adrenal hyperplasia somatic and inherited K<sup>+</sup>-channel mutations have recently been identified (35). These mutations caused increased Na<sup>+</sup> conductance and cell depolarisation leading to Ca<sup>2+</sup> entry with subsequent aldosterone production and cell proliferation.

#### *Adrenocortical carcinoma*

Adrenocortical carcinoma (ACC) is a rare tumour with an incidence in Sweden of approximately 0.1-0.2 new cases/100000 inhabitants/year (Table 1). About 50 % of ACCs are functional, mainly cortisol-producing tumours, but pure virilising or feminising syndromes can occasionally be seen (36). ACC carries a poor prognosis, with a cause-specific 5-year survival rate of 12-64 % (36-38). Better prognosis is seen in patients who present with a tumour confined to the adrenal (stage I < 5 cm, or stage II > 5 cm) (39-41). The 5-year survival is 82 % in stage I ACC (41), and 58-80 % in stage II (38, 41). However, only 2.9-6.3 (mean 4.9) % are diagnosed in stage I, and 28-50 (mean 40) % in stage II (36, 37, 41).



**Figure 3.** Prevalence of adrenal adenoma by age from 5 autopsy series (n=53520) (24, 26-29)

**Table 1.** Crude incidence rate of adrenocortical carcinoma in Sweden 1970-2009. Adapted from the Swedish National Cancer Register Database (42). \* Mean per year during the time period.

Period	Females		Males	
	New cases (n)*	Cases/million inh./year*	New cases (n)*	Cases/million inh./year.*
<b>1970-1974</b>	4.8	1.1	6.4	1.5
<b>1975-1979</b>	5.8	1.4	8.0	1.9
<b>1980-1984</b>	8.8	2.0	5.2	1.2
<b>1985-1989</b>	6.0	1.4	6.2	1.5
<b>1990-1994</b>	5.8	1.3	5.2	1.2
<b>1995-1999</b>	9.0	2.0	5.6	1.2
<b>2000-2004</b>	5.8	1.2	6.4	1.4
<b>2005-2009</b>	6.8	1.4	4.2	0.9

## Tumours of the adrenal medulla and related tumours

### *Pheochromocytoma*

Pheochromocytomas (Pheo) are rare highly vascularised tumours originating from neural crest-derived chromaffin cells of the adrenal medulla. The mean incidence in Sweden between 1958 and 2009 was stationary at 2.1 per million inhabitants per year (43) (Table 2). From 1958 through 1981 14 % of cases were detected incidentally at autopsy with a mean autopsy rate of 37 % (range 19 – 64 %) (43).

### *Paraganglioma*

Paragangliomas (PGL) are tumours closely related to Pheo originating from extra-adrenal ganglia/paraganglia (tissue expressed during fetal life). Sympathetic PGL originate from ganglia in the sympathetic nervous system along the paravertebral sympathetic trunk in the abdomen and thorax, the organ of Zuckerkandl at the root of the inferior mesenteric artery, the mediastinum, kidney and liver hila, aortic bifurcation, and urinary bladder (44-46). Parasympathetic PGL originate from parasympathetic ganglia, most commonly in the head-and-neck region (head-and-neck PGL) at the carotid bifurcation (carotid body tumour), along the vagal nerve, in the jugular foramen and in the middle ear space. Less common locations are close to the larynx, thyroid, upper mediastinum and urinary bladder (from presacral ganglia) (44, 46).

**Table 2.** Crude incidence rate of pheochromocytoma in Sweden 1970-2009. Adapted from the Swedish National Cancer Register Database (42). \* Mean per year during the time period

Period	Females		Males	
	New cases (n)*	Cases/million inh./year*	New cases (n)*	Cases/million inh./year*
<b>1970-1974</b>	10.2	2.5	7.2	1.7
<b>1975-1979</b>	9.8	2.3	5.8	1.4
<b>1980-1984</b>	8.4	1.9	10.6	2.5
<b>1985-1989</b>	10.8	2.5	11.4	2.7
<b>1990-1994</b>	10.4	2.3	7.4	1.7
<b>1995-1999</b>	10.8	2.4	9.6	2.2
<b>2000-2004</b>	11.2	2.4	10.0	2.2
<b>2005-2009</b>	8.0	1.7	7.0	1.5

Pheo and sympathetic PGL can present with symptoms related to excess CA secretion, and display different secretory patterns. Pheo can predominantly secrete A or NA; the

profile of CA-secretion is influenced by genetic factors. Sympathetic PGL, which lack the enzyme necessary for the synthesis of A from NA (phenylethanolamine-N-methyltransferase), secrete NA. Parasympathetic PGL are usually non-functioning, but can express the acetylcholine transporter.

#### *Hereditary syndromes with Pheo/PGL*

Currently there are 11 known susceptibility genes for hereditary syndromes with Pheo and/or PGL as syndromic features. *NF1* in Neurofibromatosis type 1 (NF1), *RET* in Multiple Endocrine Neoplasia syndrome type 2 (MEN2), *VHL* in Von Hippel Lindau syndrome (VHL), succinate dehydrogenase subunit genes *SDHB* (47), *SDHC* (48), *SDHD* (49), and the succinate dehydrogenase complex assembly factor 2-gene *SDHAF2* (50) in the familial paraganglioma syndromes PGL4, PGL3, PGL1, and PGL2, respectively. Recently mutations in *PHD2* (51), *SDHA* (52), *TMEM127* (53), and *Kif-1B $\beta$*  (54) have been described in association with Pheo/PGL.

Germ-line mutations have been described in 7.5 to 24 % of apparently sporadic Pheo/PGL (55-60). Risk factors for germ-line mutations guiding clinical testing include family history or age < 35 years at presentation, extra-adrenal, bilateral, multiple or malignant tumours (59, 61). The pre-test probability of hereditary disease influences the decision-making on genetic screening for mutations. The discovery of associated germ-line mutations in the individual patient mandates closer follow-up, and raises the question of pre-symptomatic screening of relatives. Effective algorithms for genetic testing are dependent on information on the prevalence of germ-line mutations in the intended target population(s).

### **Other adrenal tumours**

#### *Adrenal metastases*

Adrenal metastases are found in 13-27 % of patients with disseminated cancer at autopsy (62, 63), but isolated adrenal metastases are rare (64). Co-existing benign adrenal tumours are common also in an oncologic setting, and the likelihood that an adrenal lesion detected in a patient with extra-adrenal malignancy is a metastasis ranges from 32-73 % (65). The most common primary tumours are pulmonary, gastrointestinal or renal carcinomas (64). Surgery for adrenal metastases is performed at many centres, but only few series reporting on indications for treatment and corresponding results have been published (66-72).

#### *Miscellaneous tumours of the adrenal gland*

Other benign lesions of the adrenal gland include adrenal hyperplasia, simple cysts, myelolipomas, ganglioneuromas, adrenal haemorrhage, granulomatous disease (tuberculosis), and hemangiomas (73). Primary adrenal lymphomas are rare (74).

## ***Incidentally discovered adrenal tumours***

Since the first human computed tomography (CT) scan, performed at Atkinson Morley's Hospital in South London on October 1 1971 (75), CT has become an indispensable tool in clinical practice. It has been estimated that, only in the US, 72 million CT examinations were performed in 2007 (76).

With the use of high-resolution abdominal imaging such as CT, or magnetic resonance imaging (MRI), incidental findings (Box 1), are frequently reported (77). For instance, at CT colonography incidental extra-colonic findings have been reported in 40 % (range 12-85 %) of patients (78), 14 % of patients had further investigations due to these findings and 0.8 % had immediate treatment. Abominal aortic aneurysms, and localised (NOM0) non- colorectal cancer were detected in 0.9 % each. While some incidental findings may be of great benefit to the patient, others may be of no or uncertain importance, and may generate further, potentially harmful, diagnostic procedures.

Adrenal tumours are among the most common incidental findings at abdominal imaging, with a reported frequency of 0.4 to 5 % in populations examined with CT (79-82). These findings may represent malignant or hormone-producing tumours, but are in most cases benign and inactive. The implications of an incidentally discovered adrenal tumour (adrenal incidentaloma, AI,) and the work-up necessary are presently under debate (83, 84).

## **On terminology and definitions**

### *Adrenal incidentaloma*

The term adrenal "incidentaloma" first appeared in print in the paper *Management of the adrenal "incidentaloma"* by Geelhoed and Drury (85) from 1982. It was used to denote an adrenal "mass[...] of unknown or doubtful clinical significance". The incidental discovery was emphasised in the 2002 United States National Institute of Health (NIH) definition (3), *i.e.*, examinations performed for suspected adrenal disease and follow-up of hereditary syndromes were excluded. An important distinction was also made by excluding staging examinations for cancer; in this situation adrenal lesions would be looked for, even though not specifically asked for (Box 1). The NIH definition remains essentially unchanged in recent guidelines (86). Several authors have used the word serendipitous in conjunction to the detection of an adrenal lesion (4, 25, 79). Serendipity denotes the property of making fortunate discoveries while looking for something unrelated, or the occurrence of such a discovery during such a search (Box 2). Ahrén & Werner gave a Swedish definition of adrenal incidentaloma in 1996 (5) (Box 1).

**Box 1. Definitions of the incidentally discovered adrenal tumour (adrenal incidentaloma)**

**PubMed Medical Subject Heading- (MeSH-) database search term “Incidental Findings”**

”Unanticipated information discovered in the course of testing or medical care”  
Introduced 2003, (ncbi.nlm.nih.gov/mesh/68033162).

**Definition used in the United States National Institute of Health State-of-the-Science Report 2002 (3)**

”Clinically inapparent adrenal masses are discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to suspicion of adrenal disease and, thus, are commonly known as incidentalomas. The definition of incidentaloma excludes patients undergoing imaging procedures as a part of staging and workup for cancer.”

**Definition used by Terzolo et al. 1997 (4), for the Gruppo Piemontese Incidentalomi Surrenatici**

”*Adrenal incidentaloma* refers to any adrenal mass discovered serendipitously during an abdominal imaging evaluation performed for extra-adrenal complaints.”

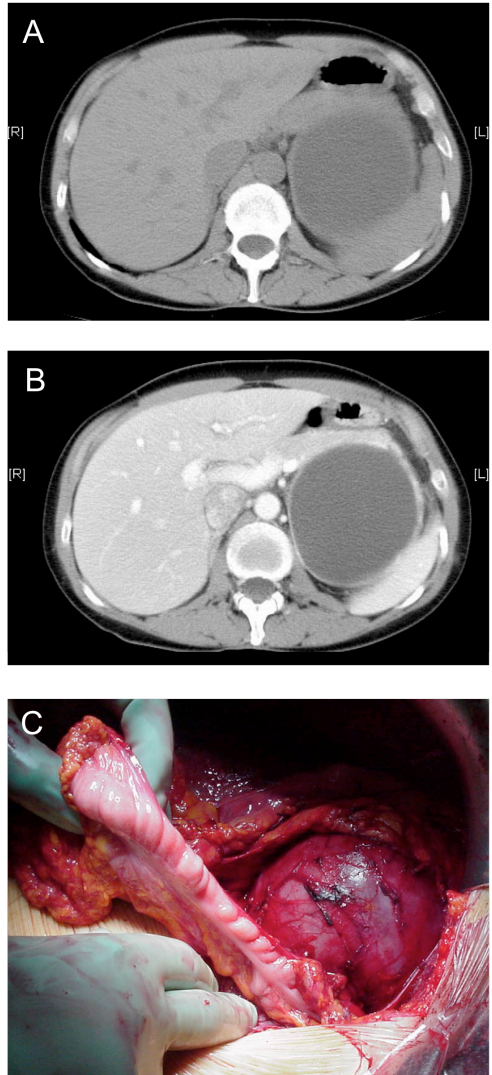
**Definition used by Ahrén and Werner 1996 (5) on behalf of the Swedish Medical Council Research Group on endocrine abdominal tumours**

”Med adrenalt incidentalom menas binjurförstoring/tumör som visualiseras, vanligen med ultraljud, DT eller MRT, under utredning av icke binjurerelaterat symtom.”

*(In english: “Adrenal incidentaloma denotes an adrenal enlargement/tumour visualized, usually with ultrasound, computed tomography or magnetic resonance imaging, during work-up of a symptom not related to the adrenal”)*

Three comments can be made about these definitions of adrenal incidentaloma. *First*, the concept of the finding being genuinely “incidental” or “serendipitous” can be questioned. As has been pointed out by Parker (87): “Some research and clinical activities are so prone to generating findings not intentionally sought that it is disingenuous to term them ‘unanticipated’ even if their precise nature cannot be anticipated in advance.” In this respect the finding of an adrenal incidentaloma is not fundamentally different if it occurs in a patient with, or without, an extra-adrenal malignancy, even if the probabilities of different underlying aetiologies vary. *Second*, in focusing on the way the adrenal lesion is discovered the term adrenal incidentaloma does not convey any biologically relevant information about the radiological finding. However, assigning a label to the finding may convey the impression that an incidentaloma is a specific condition, unrelated to other adrenal pathology. Indeed, it has

been implicated that an adrenal incidentaloma should represent a separate nosographic entity (4, 88). In clinical practice the term sometimes seems to be used in this way, or, possibly, as an equivalent to a non-functioning adrenocortical adenoma. While it is true that most incidentalomas represent benign non-secreting lesions, both malignant and/or hormone-producing tumours can be found (79, 89-92). To avoid any unnecessary ambiguity introduced by using the term "incidentaloma" in radiology reports, recent recommendations suggest that (when an adenoma can be diagnosed with imaging) the radiology report should read: "Findings consistent with a benign adenoma. If there are clinical signs or symptoms of adrenal hyperfunction, biochemical evaluation may be appropriate" (77). *Third*, the requisite that the lesion is unrelated to the patients' current complaint makes the definition of an adrenal lesion somewhat arbitrary. It has the advantage of defining a distinct clinical situation, but in some cases that distinction can be difficult and requires clinical judgement. More specifically, it requires the radiologist to see and report the lesion, and the referring physician to judge the lesion to be incidental in the present context (Figure 4A-C).



**Figure 4.** A 51 year old normotensive female undergoing CT for pain indicating a slipped disc with the finding of a large left sided cystic adrenal mass. Biochemical evaluation showed slightly elevated urinary metanephrines. After removal of a large left-sided cystic pheochromocytoma the pain disappears. Unenhanced (A) and enhanced (B) CT, intraoperative findings (C). Is this to be defined as an adrenal incidentaloma?

### Adrenaloma

To avoid the problems discussed above, the term "adrenaloma" has been proposed (93). Rather than focusing on the way the tumour was detected, it describes the adrenal localisation, and the lack of a known specific underlying pathology. However, depending



on whether the patient undergoes work-up for an adrenal tumour, diagnosed as a consequence of an examination performed for an unrelated symptom, or has overt symptoms of adrenal disease, the pre-test probabilities for malignant or hormone-producing lesions will differ, and require different work-up.

**Box 2.** *Excerpt from a letter by Sir Horace Walpole to Sir Horace Mann, January 28, 1754 (94) with the first recorded use of the word "serendipity"*

"I must tell you a critical discovery of mine *àpropos*: in an old book of Venetian arms, there are two coats of Capello, who from their *name* bear a *hat*; one of them is added a *fleur-de-lis* on a blue ball, which I am persuaded was given to the family by the Great Duke, in consideration of this alliance; the Medicis, you know, bore such a badge at the top of their own arms. This discovery I made by a talisman, which Mr. Chute calls the *Sortes Walpolianae*, by which I find every thing I want, *à pointe nommée*, whenever I dip for it. This discovery, indeed, is almost of that kind which I call *Serendipity*, a very expressive word, which, as I have nothing better to tell you, I shall endeavour to explain to you: you will understand it better by the derivation than by the definition. I once read a silly fairy tale, called 'The Three Princes of Serendip;' as their Highnesses travelled, they were always making discoveries, by accidents and sagacity, of things they were not in quest of: for instance, one of them discovered that a mule blind of the right eye had travelled the same road lately, because the grass was eaten only on the left side, where it was worse than on the right-now do you understand *Serendipity*? One of the most remarkable instances of this *accidental sagacity*, (for you must observe that *no* discovery of a thing you are looking for comes under this description,) was of my Lord Shaftsbury, who, happening to dine at Lord Chancellor Clarendon's, found out the marriage of the Duke of York and Mrs. Hyde, by the respect with which her mother treated her at the table."

*Working definition of incidentally discovered adrenal lesions – adrenal incidentalomas*

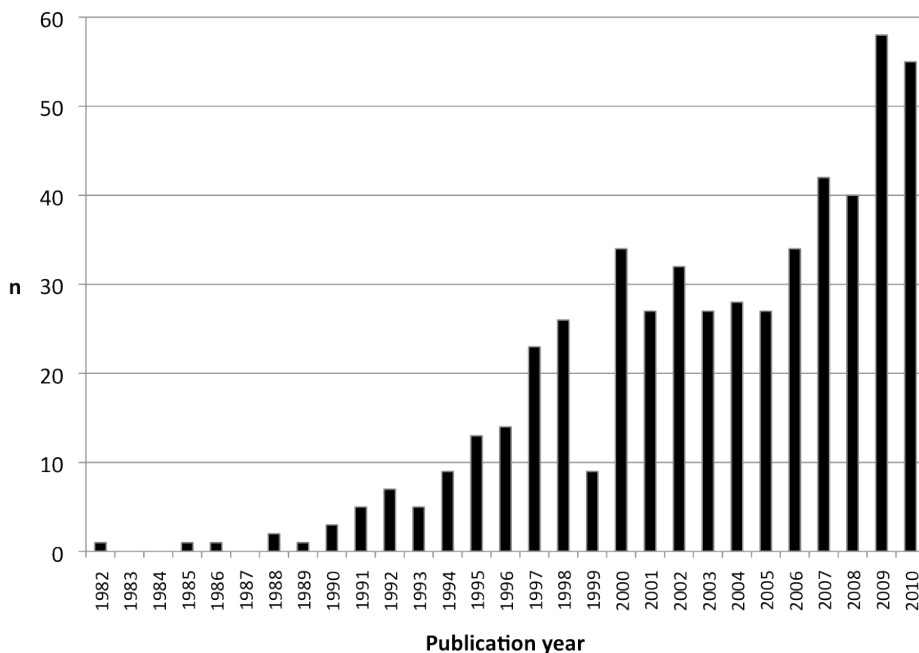
A search for "adrenal incidentaloma\*" on PubMed resulted in 514 publications (Figure 5), while a search for "adrenaloma\*" gave 11 relevant publications (search date 2011-01-27). Despite its inherent drawbacks and ambiguities the term adrenal incidentaloma (AI) was used in the present thesis according to the Swedish definition (Box 1).

### **Rationale for diagnostic work-up and follow-up in patients with adrenal incidentalomas**

More important than the definition of AI is the question: How shall we handle information nobody has asked for? The purpose of diagnostic work-up in patients with AI is to identify individuals with malignant or hormone-producing tumours. Concerns about malignancy or hormone-production developing or presenting over time motivate follow-up programmes. The implicit assumption is that the patient benefits from early (pre-symptomatic) diagnosis of these conditions. Effective algorithms for diagnostic

work-up and follow-up require information on the prevalence of AI and the proportion of patients with malignant, or hormone-producing, tumours in the intended target population.

The mean frequency of malignant and hormone-producing tumours detected in published series of patients with AI ranges from 1.9 – 4.7 % for ACCs, 0.7 – 2.5 % for metastases, 5.3-7.9 % for subclinical hypercortisolism (SH), 3.1-5.6 % for Pheo, and 0.6-1.2 % for aldosteronomas, as summarised in leading reviews (30, 83, 95, 96).



**Figure 5.** Number of publications retrieved by PubMed using the search term "adrenal incidentaloma\*", by publication year. (Search date 2011-01-27.)

The risk of malignancy developing in an AI over time seems small. Reports of ACC discovered during follow-up of AI are anecdotal. Barzon et al. (30) related two patients from their own experience; one with a functioning 90 mm ACC, which had progressed over two years from a 25 mm lesion at ultrasound; and the other with a non-functioning 60 mm ACC, which had progressed over one year from 30 mm. Further details on patient or lesion characteristics are not reported. Cofield et al. (97) reported one patient with a stationary non-functioning adrenal mass (48 mm), which after eight years presented with hormonal symptoms and disseminated ACC. Finally, Libé et al. (98) reported one patient with a growing tumour at six months follow-up, and a final diagnosis of non-Hodgkin lymphoma.

The frequency of hormone-producing tumours detected at follow-up is low, but varies according to follow-up protocols and diagnostic criteria (mainly for SH). In the nationwide Swedish study of 381 patients (90, 91), 90 patients underwent adrenalectomy at detection, of the remainder follow-up data (median follow-up 25 months) was reported for 229 patients: two patients were diagnosed with Cushing's syndrome at 10 and 36 months follow-up and one patient was diagnosed with Pheo, nine years after AI was diagnosed. Barzon et al. (99) studied 130 patients with AI and a median follow-up of 4.7 years. They saw development of SH in five patients, Cushing's syndrome in four patients, one of whom had SH at baseline, and of Pheo in one patient. Based on these data they calculated the risk of adrenocortical hyperfunction to develop from a non-functioning AI to 3.8 % after one year, and 6.6 % after five years. Of a total of eight patients with SH at baseline, one (12.5 %) developed Cushing's syndrome after one year.

The majority of patients with AI have benign, non-functioning lesions (30), which require no specific therapy. These patients do not benefit from follow-up, but may suffer from repeated investigations, and there has been concern about the psychological effects of diagnosis and follow-up (3). Information on patient-reported outcomes is important for tailoring management strategies for patients with AI. However, little research has been done on the impact on Health-Related Quality of Life (HRQoL) of a diagnosis and follow-up for AI (100-102).

Reports on the frequency and natural history of AI are heterogenous with different inclusion criteria and follow-up protocols. The applicability of these results in an unselected population subject to radiological examinations may therefore be limited (83). To resolve these issues, the need for prospective population-based studies has been underlined (3, 30).

### Is the AI malignant? – Radiological characterisation

#### *Lesion size*

For primary adrenal tumours size is an established risk factor, *i.e.* larger tumours have a greater risk of being malignant (4, 103). The sensitivity and specificity of different size thresholds for detecting an ACC have been calculated (Table 3).

**Table 3.** Sensitivity and specificity of different size thresholds for detecting ACC.

Threshold (cm)	Terzolo, 1997		Sturgeon, 2006	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
3.0	100	18		
4.0	93	43	97	52
5.0	93	64		
6.0	78	75	91	80
8.0			79	95

Sensitivity is defined as the proportion of individuals with disease correctly identified with the test (true positives/(true positives + false negatives)), and specificity as the proportion of individuals without disease correctly identified (true negatives/(true negatives + false positives)). Sensitivity and specificity are specific to the test, and independent of the prevalence of the condition studied. Clinically more useful parameters are the positive and negative predictive values (PPV and NPV). The PPV is defined as the probability that a positive test result is true (true positives/(true positives + false positives)), and the NPV as the probability that a negative test result is true (true negatives/(true negatives + false negatives)). These values are dependent on the pre-test probability of the disease in the tested population. Using a pre-test probability of 5 % (5 % of AI assumed to be malignant) Sturgeon et al. (103) calculated the PPV (probability that a tumour larger than the size threshold is an ACC) for a threshold of 4 cm to 10 %, increasing to 47 % for 8 cm. The pre-test probability in an unselected population undergoing radiological examinations is reasonably much lower.

#### *Unenhanced CT*

In 1945 Russi et al. (24) noted a predominance of cells with medium-sized and large-size lipid vacuoles in adrenal adenomas, rendering them paler than adjacent cortex on visual inspection. Korobkin et al. (104) showed that the lipid content in adrenal adenomas had an inverse linear correlation to CT attenuation. In 1978, Shaner et al. (105) reported four patients with adenomas with low attenuation; this finding was later corroborated by Päivansalo et al. (106) and Miyake et al. 1989 (107). Subsequently several authors showed that attenuation, measured in Hounsfield Units (HU), on unenhanced CT was useful to distinguish benign from malignant lesions (108-112). In a meta-analysis, the sensitivity for identifying a benign lesion using a threshold of  $\leq 10$  HU on unenhanced CT was 71 % with a specificity of 98 % (113). Using a  $\leq 10$  HU threshold for distinguishing benign adrenal tumours on unenhanced CT was endorsed by the NIH State-of-the Science report in 2002 (3), and its utility has been repeatedly confirmed (114-116). However, about 30 % of benign adenomas are lipid-poor and cannot be reliably distinguished from malignant lesions on unenhanced CT (113).

#### *Dynamic CT with intravenous contrast and washout characteristics*

Both malignant and benign adrenal tumours display increased attenuation (enhancement) after administration of intravenous contrast, but both lipid-rich and lipid-poor adenomas tend to wash out the contrast material faster than malignant lesions (117-119). By obtaining enhanced series in the portal venous phase and a delayed scan, the degree of washout can be determined (120).

Caoili et al. (120) evaluated a protocol consisting of an unenhanced CT scan, followed by an enhanced scan and a delayed scan after 15 minutes for indeterminate cases ( $HU > 10$ ). With an absolute washout ( $(HU \text{ on enhanced scan} - HU \text{ on delayed scan}) / (HU \text{ on enhanced scan} - HU \text{ on unenhanced scan})$ ) threshold of  $> 60$  % (121) the sensitivity and specificity for detecting a benign lesion was 98 and 92 %, respectively. Using relative washout ( $(HU \text{ on enhanced scan} - HU \text{ on delayed scan}) / HU \text{ on enhanced scan}$ ) with a threshold of  $> 40$  % (119, 121), the sensitivity and specificity was slightly lower (82 and 92 %, respectively) (120). High sensitivity and specificity has also been demonstrated with delayed scans after 10 min, with relative washout thresholds of 37.5 - 50% (122, 123), but this has recently been questioned (124).

### *Magnetic resonance imaging*

MRI with chemical shift technique, using signal intensity loss on opposed-phase versus in-phase imaging can distinguish lipid rich adenomas from lipid-poor lesions with approximately the same performance as unenhanced CT (112, 125-129).

### *Fine-needle aspiration cytology*

Conventional fine-needle aspiration cytology of adrenal tumours can help to distinguish between primary and metastatic lesions, but can rarely differentiate between benign and malignant adrenal primary tumours. In most cases cytology does not influence management (130), but may be of value in selected cases. The diagnosis of a suspected Pheo must be ruled out biochemically prior to aspiration to avoid the risk of haemorrhage or a potentially fatal hypertensive crisis (130, 131).

### *Comprehensive radiological characterisation*

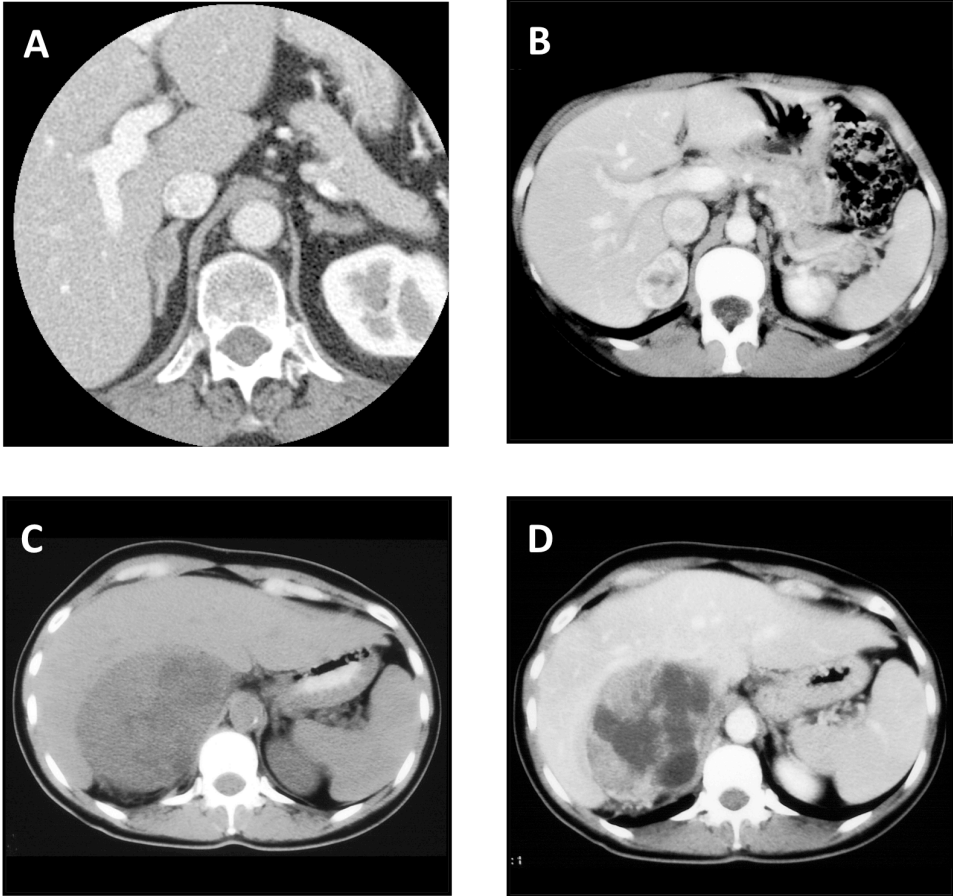
Unenhanced CT, combined with washout characteristics, is effective for discerning benign from malignant tumours in almost all cases. Apart from size, attenuation and washout characteristics, other features such as stability over time from previous imaging, margins and internal structure of the lesion on unenhanced scans (106) are helpful in the characterisation. CT of adrenal lesions is exemplified in Figure 6. MRI, PET/CT or other functional imaging (see below) have limited availability, and seem to offer no advantage to CT in the screening situation.

## **Is the AI hormone-producing? – Functional characterisation**

### *Screening for subclinical hypercortisolism*

SH, also known as subclinical Cushing's syndrome, is the most commonly described endocrine abnormality in patients with AI. It is characterised by subtle, dysregulated (ACTH-independent) cortisol secretion from an adrenocortical adenoma without overt signs of Cushing's syndrome (86).

Diagnostic criteria for SH aim at demonstrating autonomous cortisol secretion. Most authors have advocated the use of the 1 mg dexamethasone suppression test (1 mg-DST) for screening. 1 mg of dexamethasone is administered in the evening (at 10 p.m.) and serum cortisol is measured the following morning (at 8 a.m.). The NIH State-of-the-Science report from 2002 (3) and recent American Guidelines (86) recommended a serum cortisol threshold of >140 nmol/l (5.0 µg/dl) for a positive test (non-suppressibility). Aiming to increase sensitivity (thus accepting decreased specificity) lower thresholds (132) down to 50 nmol/l (1.8 µg/dl) (32, 133) have been suggested. For a diagnosis of SH Mantero et al. (89) required at least two abnormal tests of hypothalamic-pituitary-adrenal-axis (HPA-axis) function (elevated or high normal 24 h urinary free cortisol levels, loss of diurnal cortisol rhythm, suppressed ACTH, non-suppressible cortisol (>140 nmol/l) on 1 mg-DST, or blunted ACTH-response to corticotropin releasing hormone (CRH-test)). Others (134, 135) have used the low-dose dexamethasone suppression test (0.5 mg orally every 6 h for 48 h) in conjunction with at least one other abnormal result of HPA-axis function to establish the diagnosis of SH. Need for postoperative cortisol supplementation is the ultimate proof of the diagnosis (136), but is not a useful criterion in the initial evaluation.

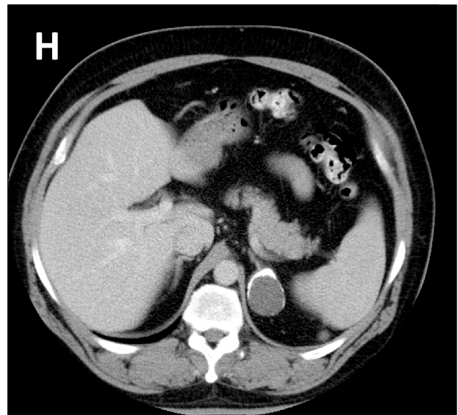
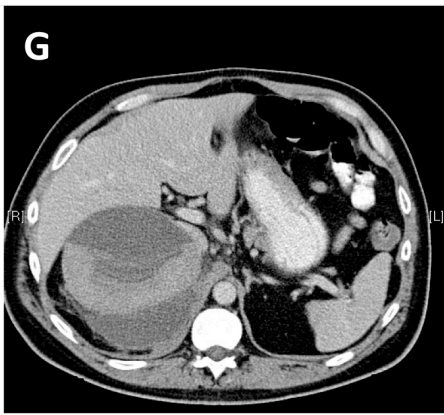
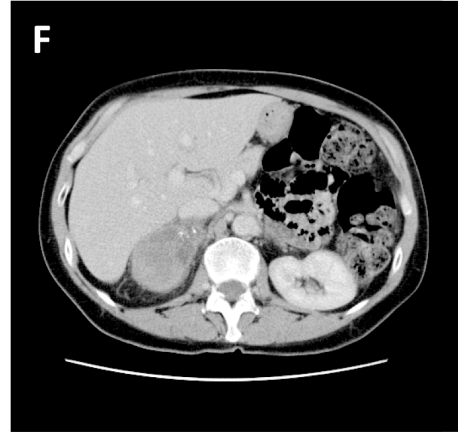
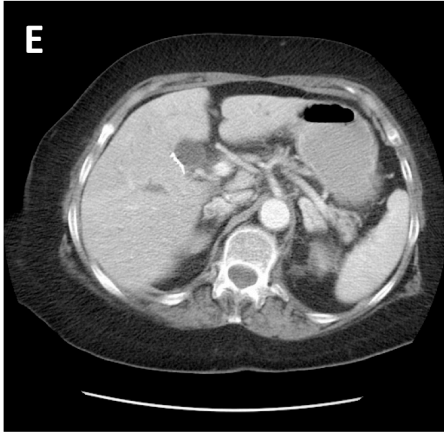


**Figure 6.** CT of adrenal lesions (E-H opposite side). A: Right sided adrenal adenoma. B: Right sided Pheo. C & D: ACC. E: Bilateral hyperplasia in Cushing's disease. F: Right sided metastasis of lung cancer. G: Right sided adrenal haemorrhage. H: Left sided calcified cyst. All intravenous contrast enhanced CT except C.

Variable absorption and metabolism of dexametasone influence the results of the 1 mg-DST. Hepatic enzymatic clearance of dexametasone, mediated by CYP 3A4, shows inter-individual variation, is induced by alcohol and several drugs, *e.g.* phenytoin and carbamazepine, and is inhibited by other drugs, *e.g.* fluoxetine and diltiazem (32). Estrogens increase the concentration of cortisol-binding globulin, leading to false positive 1 mg-DST in 50 % of women using oral contraceptives (32).

#### *Screening for primary aldosteronism*

The ratio between plasma aldosterone concentration and plasma renin activity (aldosterone renin ratio, ARR) has been widely used as a screening tool to detect PA in



hypertensive patients (137). ARR is advocated as a simple test for outpatient use, requiring a minimum of preparations. Hypokalemia blunts aldosterone secretion and patients with hypokalemia should be supplemented. Use of mineralocorticoid receptor antagonists, (*e.g.* spironolactone and eplerenone,) and amiloride may give false negative results, and should be discontinued at least 6 weeks prior to testing (137). The cut-off values employed for ARR vary depending on the laboratory and assays used. Using a ratio carries the risk of false positives on the basis of a low renin with normal aldosterone levels, and many centres require an elevated or high-normal aldosterone (>416 pmol/l) in combination with elevated ARR for a positive test result (138).

In 19 studies on patients with resistant hypertension, or hypokalemia, reviewed by Kaplan (139) the prevalence of elevated ARR ranged from 5.5 to 39 %. Lack of suppression to salt loading (confirmatory test) was seen in 26 - 95 % (mean 60 %), and aldosterone-producing adenomas were found in 0 - 66 % (mean 18 %) of patients with elevated ARR.

Only few studies report on ARR in the context of AI. In the study by Mantero et al. (89) ARR was measured in 493 normokalemic patients with AI, and PA was diagnosed in 16 cases; all had elevated ARR and moderate hypertension. Bernini et al. (140) determined

ARR in 90 normokalemic hypertensive patients and 35 normokalemic normotensive patients with AI using the saline infusion test, or the captopril test, for confirmation. Two normotensive patients had false positive ARR. Eight hypertensive patients had elevated ARR. Six of these were investigated further; two had normal confirmatory test results, while four showed partial or total aldosterone non-suppressibility, (one of these was surgically cured and three, with bilateral lesions, were treated medically). Vierhapper (141) evaluated ARR in 100 normotensive and 169 hypertensive patients with AI. In the normotensive group 2/100 had elevated ARR but normal confirmatory tests. In the hypertensive group 14 patients had elevated plasma aldosterone and elevated ARR. Of these six had PA (five with pronounced hypokalemia), and three were operated and cured. Current guidelines recommend ARR as a screening test for PA in hypertensive patients with AI (86, 142).

#### *Screening for pheochromocytoma*

Most Pheo secrete A and/or NA. Plasma free metanephrines, 24 h urinary excretion of CA, total or fractionated metanephrines, and VMA have been used to demonstrate CA hypersecretion. The test with the best sensitivity (97-99 %) is plasma free metanephrines. Specificity is high, but less than for urinary total metanephrines (143) (Table 4). Using pooled data from three studies, Sawka et al. (144) estimated the post-test probability of Pheo in a patient with AI and elevated free plasma metanephrines (assuming a 5.1 % prevalence of Pheo in AI-patients (96)) to 23.7 %. In hypertensive patients plasma free metanephrines followed by urinary total metanephrines and fractionated CA in equivocal cases may be a more cost-effective case-finding approach than plasma metanephrines alone (145). Plasma metanephrines are recommended as the initial test for Pheo in patients with AI (86). However, it should be noted that the test has limited availability, and urinary fractionated metanephrines (96-97 % sensitivity) is an acceptable alternative (146).

**Table 4.** Sensitivity and specificity of different plasma and urine analyses of catecholamines and their metabolites in detecting pheochromocytoma. Modified from Lenders et al., (143).

	Sensitivity (%)		Specificity (%)	
	Sporadic	Hereditary	Sporadic	Hereditary
Plasma free metanephrines	99	97	82	96
Plasma catecholamines	92	69	72	89
Urine fractionated metanephrines	97	96	45	82
Urine catecholamines	91	79	75	96
Urine total metanephrines	88	60	89	97
Urine vanillylmandelic acid	77	46	86	99

At CT Pheo have no typical features, and may imitate both benign adrenocortical adenomas and malignant lesions (147). At MRI a bright signal on T2-weighted images is highly suggestive of Pheo (148), but this sign is insensitive and may also be present in adrenocortical tumours (149). Thus, the diagnosis of Pheo relies on biochemical testing.



## Role of functional imaging

Scintigraphy using [<sup>131</sup>I]-6β-iodomethyl-19-norcholesterol (NP-59) and [<sup>123</sup>I]-meta-iodo-benzyl-guanidine ([<sup>123</sup>I]-MIBG) has been used in the characterisation of patients with AI (150). Barzon et al. (151) correlated discordant uptake of NP-59 (no uptake by the tumour) with malignancy, and 5/6 Pheo were [<sup>123</sup>I]-MIBG positive, with a PPV of 71 %. No comparison with CT was made. The first introduced MIBG scintigraphy used [<sup>131</sup>I] as radionuclide. [<sup>123</sup>I] is more expensive, has to be synthesised shortly before administration and is not available in all countries, but results in superior image quality. Still [<sup>131</sup>I]-MIBG may have certain advantages since it allows delayed imaging with visualisation of low-uptake lesions not detected against high background activity, and planning of [<sup>131</sup>I]-MIBG-radiotherapy in case of malignant Pheo/PGL (152). Limitations for the use of scintigraphy includes low image resolution for small lesions, limited availability, need for iodine supplementation and a significant lead time between injection and imaging (150).

Positron-emission tomography combined with CT using the radiolabelled glucose-analog fluorodeoxyglucose ([<sup>18</sup>F]-FDG-PET/CT) has been performed to differentiate between benign and malignant adrenal lesions in patients with extra-adrenal malignancy with high sensitivity and specificity (153), and can also be used in the re-staging of patients with adrenal metastases to evaluate extra-adrenal disease (154). Positron-emission tomography with the radiolabelled 11β-hydroxylase inhibitor metomidate ([<sup>11</sup>C]-MTO-PET/CT) has been used to distinguish tumours of adrenocortical origin from other adrenal tumours (155). [<sup>11</sup>C]-hydroxyephedrine, [<sup>11</sup>C]-epinephrine, [<sup>11</sup>C]-hydroxytryptophan, [<sup>18</sup>F]-fluorodopamine ([<sup>18</sup>F]-FDA), and [<sup>18</sup>F]-fluoro-dihydroxyphenylalanine ([<sup>18</sup>F]-DOPA) have been used to visualise adrenomedullary tissue (156). Timmers et al. (157) compared [<sup>123</sup>I]-MIBG scintigraphy with CT, MRI and PET/CT using [<sup>18</sup>F]-FDA, [<sup>18</sup>F]-DOPA, and [<sup>18</sup>F]-FDG for localisation of Pheo/PGL. In non-metastatic disease the ability to localise Pheo/PGL was investigated using histopathology as gold standard. All lesions were identified by CT and MRI, 88 % by [<sup>18</sup>F]-FDG, 81 % by [<sup>18</sup>F]-DOPA, and 78 % each by [<sup>18</sup>F]-FDA and [<sup>123</sup>I]-MIBG. The differences between the functional imaging modalities were not statistically significant. The false positive rate was 10 % for [<sup>18</sup>F]-FDG, and 5 % for [<sup>18</sup>F]-FDA and [<sup>123</sup>I]-MIBG, respectively. In metastatic Pheo/PGL [<sup>123</sup>I]-MIBG had a sensitivity of 57 % compared to 76 % for [<sup>18</sup>F]-FDA and 74 % for [<sup>18</sup>F]-FDG. In patients with *SDHB*-related Pheo/PGL [<sup>18</sup>F]-FDG-PET/CT has a high sensitivity to detect metastatic disease (158). The use of PET/CT is also hampered by limited availability.

In the primary evaluation of patients with AI functional imaging add little to basal biochemical and radiological evaluation, but may be of value for further work-up in selected cases.

## ***Aims of the thesis***

- To investigate the frequency of adrenal incidentalomas in an unselected population undergoing radiological examinations
- To evaluate the clinical outcome of a standardised work-up and follow-up programme for adrenal incidentalomas
- To evaluate the patient-perceived impacts of the diagnosis and follow-up of an adrenal incidentaloma
- To investigate the outcome of surgery for adrenal metastases and identify positive prognostic factors for survival
- To investigate the prevalence of germ-line mutations in a population from Western Sweden with apparently sporadic pheochromocytoma or abdominal paraganglioma

## Patients and methods

### *The study of adrenal incidentaloma in Western Sweden (Paper I-III)*

#### **Study population**

During 18 months (from October 16 2002 through April 15 2004) all patients  $\geq 18$  years of age with an AI, detected by CT, MRI or ultrasonography, were prospectively reported from all departments of radiology (n=19) in Western Sweden (Figure 7). Patients with clinical symptoms or signs related to the adrenals, patients referred specifically for a radiological examination of the adrenal(s), and patients with known adrenal enlargement or tumour were not included. At 15 of the participating radiology departments abdominal CT examinations from a randomly selected part of the inclusion period (n=3827) were reviewed for adrenal mass lesions or enlargements. In total, 534 patients were assessed for eligibility. Eligible patients were included in a standardised two-year follow-up programme.

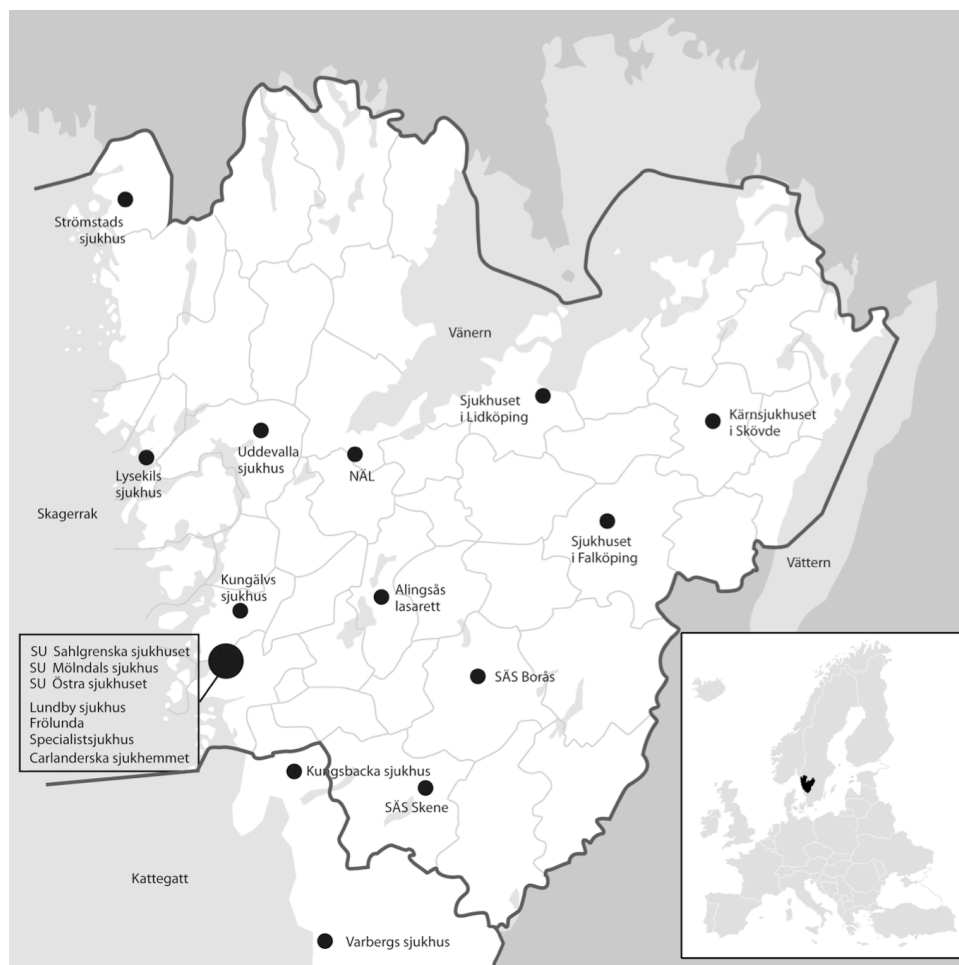
In paper I, focusing on AI detected with CT, 339 patients (193 females; mean age 69 years, range 30-94 years) with prospectively reported and verified AI were compared with 177 patients identified during systematic re-evaluation (of which 53 also had been prospectively reported).

In paper II, all patients from the total study population without signs of extra-adrenal malignancy at detection of AI (n=226) were studied.

In paper III, the study population comprised all patients from the total study population who were alive and who had completed the two-year follow-up programme without evidence of adrenal malignancy, or hormone-producing tumour, by November 2007 (n=145).

#### **Methods**

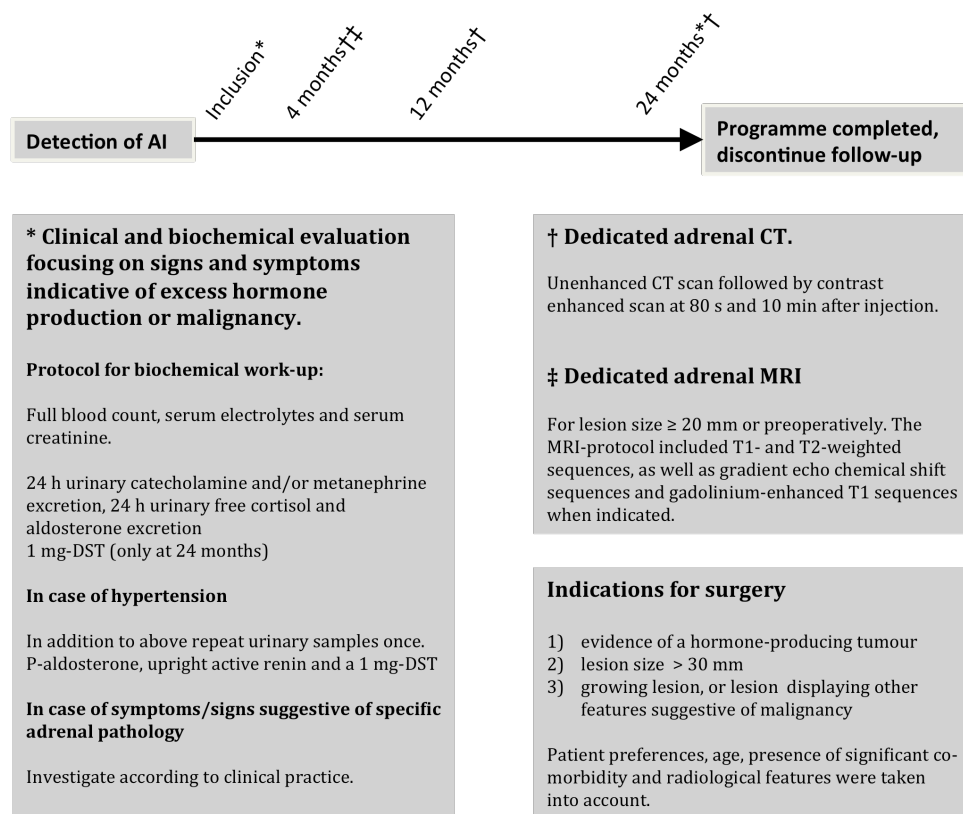
The algorithm for clinical and radiological follow-up (paper II-III) is shown in Figure 8. In an effort to avoid underreporting all incidentally discovered adrenal lesions, regardless of size and clinical situation, could be reported. However, all radiological examinations were reviewed at the main study centre, and only lesions larger than the normal limits for the adrenal glands as defined by Vincent et al. (159) (Table 5) were accepted. Radiological inter-observer agreement was assessed (160) (paper I). Clinical data were retrieved from case-report forms and hospital files, and the study population was cross-checked against the National Cancer Register (NCR) for a diagnosis of malignancy registered up to 3 months after detection of AI (paper I-III) and during follow-up (paper II-III). Causes of death for patients dying during the study period were retrieved from the Swedish Cause of Death Register (paper II).



**Figure 7.** The region of Western Sweden and Northern Halland with all participating radiology departments ( $n=19$ ). During the study period 17 departments offered CT service (15 with abdominal CT). Adapted from (161), with permission.

In paper I two patient categories were identified: 1) Patients who were diagnosed with an extra-adrenal malignancy at, or < 5 years before detection of the AI, and 2) patients who had no extra-adrenal malignancy, including patients with a history of extra-adrenal malignancy diagnosed > 5 years before detection of the AI, but no signs of present extra-adrenal malignancy. The allocation of patients with a history of extra-adrenal malignancy, but no signs of extra-adrenal malignancy at detection, was motivated by the assumption that a malignancy diagnosed > 5 years previously was less likely to have current clinical impact than a malignancy diagnosed < 5 years before detection of AI.

The focus in paper II was on the clinical situation of AI in a patient without extra-adrenal malignancy. Patients with a history, but no present signs of extra-adrenal malignancy, were included but analysed separately.



**Figure 8.** *The Study of Adrenal Incidentaloma in Western Sweden – Study algorithm*

In paper II, lesions were radiologically classified as benign if they had features consistent with adenoma/hyperplasia (homogenous, well circumscribed, lipid-rich ( $\leq 10$  HU on unenhanced series), or with an absolute washout of  $> 50\%$  on delayed scan after 10 minutes (122), or other typical benign characteristics (e.g. thin-walled cyst, myelolipoma, or adrenal haemorrhage) (73). At MRI, lesions were classified as benign if they showed signal intensity decrease on opposed-phase images, as compared to in-phase images (125, 128). Lesions not fulfilling these criteria, or with incomplete imaging information, were classified as indeterminate. Changes in lesion size were assessed using criteria adopted from RECIST, version 1.1. (162). Growth was defined as an increase in lesion transverse diameter  $> 20\%$  (minimum  $> 5$  mm), and a decrease in size as a decrease in transverse diameter  $> 30\%$ . A stationary indeterminate lesion was defined as a homogenous, well-circumscribed lesion, stationary in size over  $\geq 12$  months

time. Signs of excess hormone production at evaluation prompted further investigation according to standard endocrinological practice.

**Table 5.** *The size of normal adrenal glands on computed tomography, after Vincent et al. (159)*

	Right adrenal	Left adrenal
Maximum width mm (SD)	6.1 (2)	7.9 (2.1)
Medial limb width mm (SD)	2.8 (0.8)	3.3 (0.9)
Lateral limb width mm (SD)	2.8 (0.6)	3.0 (1.0)

In paper III, two interviews with patients with AI were performed, and a recurring theme of anxiety – relief was identified. Based on these interviews, and consultations with a clinical expert group consisting of endocrinologists and endocrine surgeons from Western Sweden with experience in treating patients with AI, an Adrenal Incidentaloma Impact Questionnaire (AIIQ) was constructed (Appendix 1). The AIIQ was face validated, and used together with the Swedish version of the Short Form 36 (SF-36) (163) and the Hospital Anxiety and Depression Scale (HADS) (164). The SF-36 is a 36 item survey covering eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The HADS consists of two 7-item subscales evaluating anxiety (HADS-A), and depression (HADS-D). Established and validated cut-off values (<8 non-cases, 8-10 possible cases, and >10 probable cases) for each subscale were used (165). AIIQ responses were coded and data was structured using an exploratory factor analysis. Summated Likert scales were constructed for the resulting factors and correlated (Pearson's rho) with the domains of SF-36 and HADS. To investigate response patterns and correlations with clinical background data, further statistical analyses were performed with non-parametric methods for categorical and ordinal data, and with oneway ANOVA for continuous data.

### ***Surgery for adrenal metastasis (Paper IV)***

#### **Study population**

The study population comprised a consecutive series of patients undergoing adrenalectomy for metastasis to the adrenal gland at Sahlgrenska University Hospital from 1996 through 2007. Patients with direct extension of a primary tumour into the adrenal gland, or renal cell carcinoma with ipsilateral synchronous adrenal metastasis, were not included.

#### **Methods**

Information on patient gender, time of surgery, last follow-up or death, age at surgery, clinical presentation (synchronous or metachronous tumour, disease-free interval (DFI), previous metastasectomy), type of operation (open or laparoscopic), completeness of

resection, size and histopathological diagnosis of the metastasis was gathered through patient records from our unit and referring hospitals. A metastasis was regarded as synchronous/metachronous if detected within/after 6 months from primary surgery. DFI was calculated from time of latest tumour manifestation to detection of the adrenal metastasis. Adrenalectomy for potential cure was defined as a local R0-resection (makro- and microscopically tumour-free resection margins) without evidence of residual tumour at other sites. All histopathological reports were reviewed, and information on causes of death was retrieved from the Swedish Cause of Death Register.

Overall and disease-free survival was calculated from time of adrenalectomy to death, or recurrence, using the Kaplan-Meier method. Univariate comparisons of survival with respect to different background variables were performed with the log-rank test. Multiple stepwise Cox-regression was used to construct a model relating survival to risk factors. The results given are from the final model. A p-value < 0.05 was considered statistically significant.

### ***Germ-line mutations in Pheo/abdominal PGL with apparently sporadic presentation (Paper V)***

#### **Study population**

From the western health-care region in Sweden (comprising the region of Västra Götaland and the municipalities Varberg, Falkenberg and Kungsbacka, total population 1.7 million inhabitants) all patients with Pheo/PGL registered in the NCR between 1958 and 2009 were identified. Search terms were: ICD-7 localization codes 195.0 (adrenal medulla) and 195.7 (paraganglia); morphology codes 441 (benign Pheo/PGL) and 446 (malignant Pheo/PGL or malignant neuroendocrine tumour). Only patients with histopathologically verified disease were included.

#### **Methods**

Patients were characterised using register data, hospital records and clinical interviews. Sporadic presentation was defined as a negative family history and absence of syndrome manifestations associated with MEN2, NF1 or VHL at diagnosis. Malignancy was defined as presence of metastases (chromaffin tissue present at sites where chromaffin tissue is not normally found (44)) at the time of diagnosis or during follow-up. All patients alive who had been treated for Pheo, or abdominal PGL, with sporadic presentation were invited to genetic screening, which started in the spring of 2006.

From purified leucocyte DNA the presence of point mutations and deletions was investigated using conventional sequencing (166) and Multiplex Ligation-dependent Probe Amplification (MLPA) (167) in the following order: 1) *SDHB* exon 1-8, *SDHD* exon 1-4 and *VHL* exon 1-3 were sequenced; 2) In patients with negative sequencing results in *SDHB*, *SDHD* and *VHL*, *RET* exon 10, 11, 14 and 16 were sequenced; 3) In patients negative after testing for *RET*-mutation MLPA analysis of *SDHB*, *SDHC*, *SDHD* and *VHL* was performed.

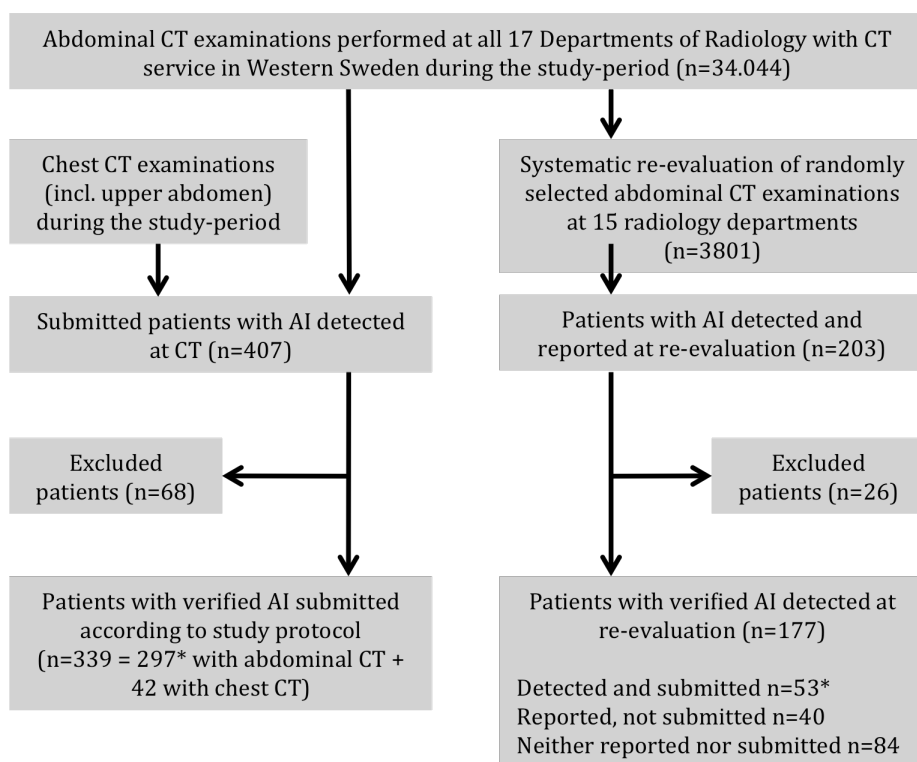
Fractionated plasma metanephrines, 24 h urinary fractionated CA excretion and/or 24 h urinary fractionated metanephrine excretion were used for biochemical follow-up.



## Results

### *The frequency of AI in an unselected population undergoing radiological examinations (paper I)*

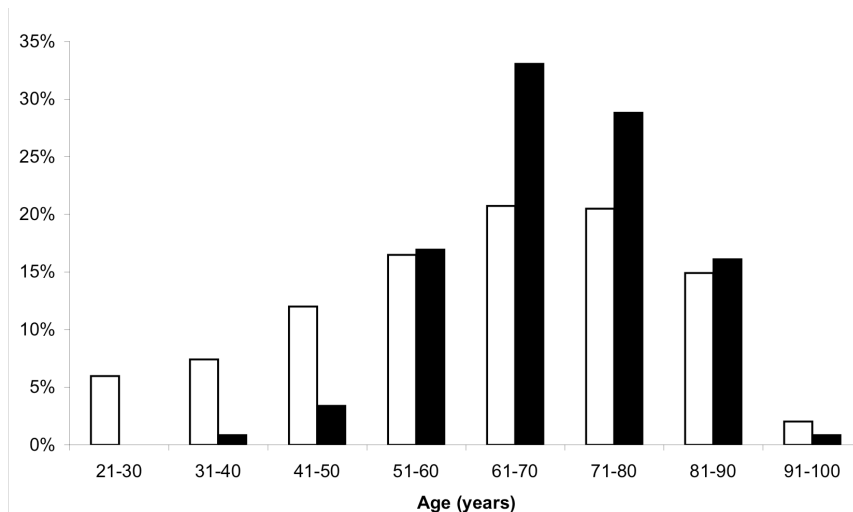
From October 16 2002 through April 15 2004, 34044 abdominal CT examinations were performed in Western Sweden. During this period 297 patients with AI detected at abdominal CT were prospectively reported and fulfilled the inclusion criteria (Figure 9 left). This corresponds to a frequency of AI at abdominal CT of 0.9 %. Including 42 patients detected at chest CT, 151 patients (100 females, mean age 69 years, median 70 years, range 30 – 89 years) did not have a previous history of malignancy, or (n=16) had a diagnosis of malignancy > 5 years prior to detection of the AI, and no signs of present extra-adrenal malignancy. The other 188 patients (mean age 69 years, median 69 years,



\* Overlapping.

**Figure 9.** *Patients with AI detected according to study protocol and at re-evaluation, paper I.*

range 33 – 94 years) had extra-adrenal malignancy < 5 years prior to, or at detection of AI. Submitted patients with verified AI were older compared to a representative sample of patients undergoing abdominal CT during the study period (Figure 10). The detection of AI started in the 4<sup>th</sup>, and peaked in the 7<sup>th</sup> decade of life.



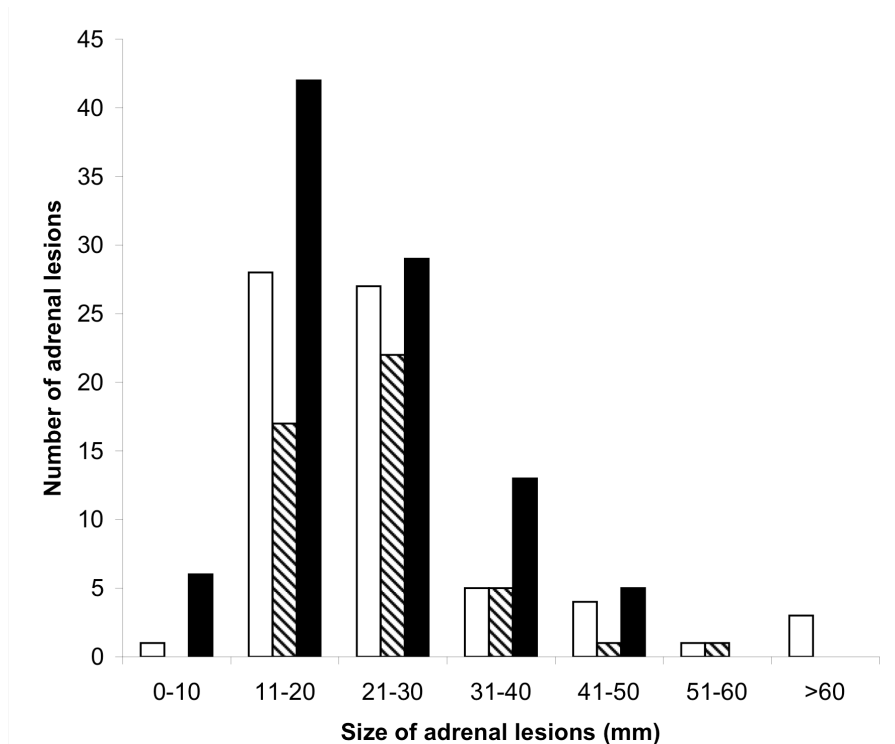
**Figure 10.** Relative age distribution of reported patients compared to a representative sample undergoing abdominal CT during the study period. Open bars: Abdominal CT performed at the main study centre, one regional and one local hospital (n=11 289). Closed bars: All reported patients from these hospitals with AI detected at abdominal CT (n=339)

3801 consecutive abdominal CT scans during a randomly selected part of the inclusion period at all but one (county hospital) of the participating hospitals performing abdominal CT were reviewed, and AI was verified in 177 patients (Figure 9 right). Of these, only 30 % had been detected and reported according to study protocol. No difference was seen with regard to lesion size between submitted patients and patients detected at re-evaluation (Figure 11), and the indications for the examinations were similar. The mean frequency of AI at re-evaluation was 4.5 % (range 1.8 – 7.1 % between hospitals) (Table 6).

**Table 6.** Frequency of adrenal lesions at re-evaluation (paper I)

	No of CT exams/hospital during study period*	No of re-evaluated CT exams/hospital*†	Adrenal lesion frequency (%) at re-evaluation*
Total (n=16)	2128(338-7819)	253(68-438)	4.5 (1.8-7.1)

\* Mean (range). †Fifteen of the 17 hospitals participated in the re-evaluation study, one hospital did not submit any cases, and was not included in the total.



**Figure 11.** Size distribution of adrenal lesions in the re-evaluation study (paper I). Open bars: Submitted cases (n=69). Hatched bars: Mentioned in the local radiology report, but not submitted (n=46). Closed bars: Neither mentioned, nor submitted (n=94).

### ***The outcome of a standardised follow-up programme for AI (paper II)***

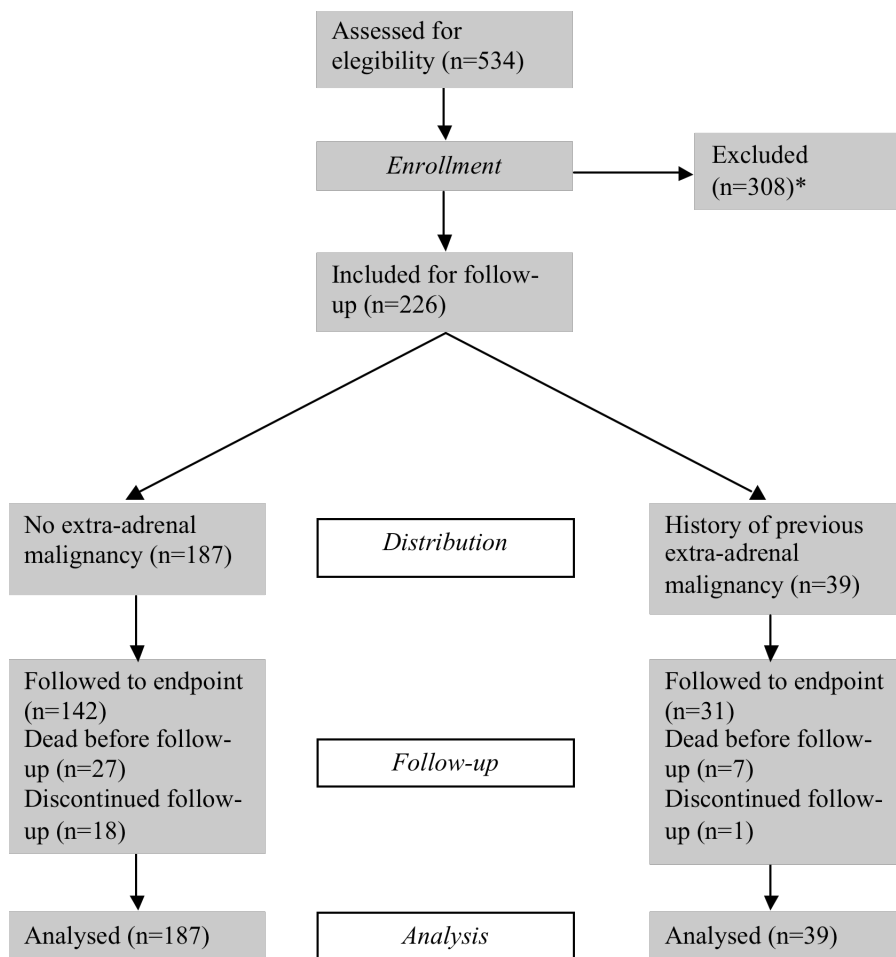
In total, 534 patients were assessed for eligibility (Figure 12), and 226 patients (mean age 76 years, 62 % females; mean size of AI 24.8 mm; 21 % bilateral) were included for follow-up. Of these 39 had been treated for malignant disease previously, but had no signs of extra-adrenal malignancy at the time of inclusion (mean time from diagnosis of extra-adrenal malignancy to inclusion 8.9 years (median 6.4 years, range 1 to 42 years). For baseline characteristics see Table 7.

The mean follow-up time was 19.0 months (18.6 months in patients without, and 21.3 months in patients with a history of extra-adrenal malignancy). Outcome of follow-up is summarised in Table 8.

Fifteen patients (6.6 %) were operated on suspicion of hormone-producing or malignant tumours (Table 9). Of these, four underwent surgery after initial work-up for suspected hormone-producing tumour (primary hyperaldosteronism (n=3), juxtaadrenal paraganglioma (n=1)). All had clinically evident disease at the baseline examination. One patient had elevated epinephrine levels at the 2-year follow-up visit, and a  $[^{123}\text{I}]\text{-MIBG}$ -

scintigraphy showed uptake concordant with the lesion. He was operated on suspicion of a Pheo, but histopathology revealed an adrenocortical adenoma.

Ten patients were operated for suspected malignancy after initial evaluation due to tumour size (mean size 47.3 mm, median 40.5 mm, range 31-100 mm) (Table 9), four of these also had additional radiological features indicating possible malignancy. One of the ten patients had a history of previous malignancy, and in this case a metastasis of a renal cell carcinoma was diagnosed; the other nine had benign histopathology. Three of the ten patients had elevated 1 mg-DST (two with unilateral, and one with bilateral lesions). All three required postoperative corticosteroid replacement that could be discontinued in the patients with unilateral lesions after 9 and 14 months, respectively.



**Figure 12.** Study overview paper II. \* Reasons for exclusion: Extra-adrenal malignancy at detection (n=217), previously known adrenal lesion (n=31), no adrenal lesion confirmed at review (n=22), examination for adrenal disease (n=3), no consent (n=35)

**Table 7. Baseline characteristics of included patients (paper II)**

Characteristic	History of extra-adrenal	
	No extra-adrenal malignancy	malignancy
<b>Subjects, n (%)</b>	187 (100)	39 (100)
Mean age, years (median, range)	67 (68, 23-91)	68 (70, 39-86)
Females, n (%)	111 (59)	30 (77)
<b>Place of detection, n (%)</b>		
University hospital	34 (18)	12 (31)
County hospital	83 (44)	16 (41)
Local hospital	70 (37)	11(28)
<b>Mode of detection, n (%)</b>		
Computerized tomography	170 (91)	38 (97)
Ultrasound	12 (6)	0 (0)
Magnetic resonance imaging	5 (3)	1 (3)
<b>Lesion characteristics</b>		
Mean size, mm (median, range)	24.1(22, 8-56)	23.2 (21, 10-100)
Bilateral, n (%)	43 (23)	8 (20)
<b>Diagnosis at detection*, n (%)</b>		
B Infection	2 (1)	/
D 00-48 Benign neoplasms	5 (3)	2 (5)
D 50-89 Blood	2 (1)	/
E Endocrine	4 (2)	/
F Mental/behavioural	1 (1)	/
I Circulatory	32 (17)	4 (10)
J Respiratory	10 (5)	2 (5)
K Digestive	71 (38)	9 (23)
M Musculoskeletal	9 (5)	/
N Genitourinary	11 (6)	/
R Symptoms	23 (12)	7 (18)
S Trauma	9 (5)	1 (3)
Y External causes	4 (2)	/
Z Control after therapy	4 (2)	14 (36)
<b>Other disease, n (%)</b>		
Hypertension	91 (49)	8(21)
Diabetes mellitus	32 (17)	2 (5)
Cardiovascular disease	51 (27)	9 (23)
Hyperlipidemia	28 (15)	4 (10)
Osteoporosis	12 (6)	5 (13)
BMI (kg/m <sup>2</sup> ) > 25†	51 (27)	9 (23)
<b>Type of malignancy, n (%)</b>		
Head and neck	/	1 (3)
Thyroid	/	1 (3)
Upper gastrointestinal	/	3 (8)
Colorectal	/	4 (10)
Lung	/	2 (5)
Breast	/	12 (31)
Malignant melanoma	/	1 (3)
Urological	/	7 (18)
Gynaecological	/	5 (13)
Multiple cancer diagnoses	/	3 (8)

\* Result of the work-up for the complaint leading to the radiological examination, grouped in chapters according to ICD-10. † BMI data available on 139 patients without extra-adrenal malignancy and 30 patients with history of extra-adrenal malignancy.

**Table 8.** Results of the 2-year follow-up programme (paper II)

Group	Outcome	N	Mean follow-up time (median, range), months
<b>No history of extra-adrenal malignancy</b> <i>n=187</i>	Adrenalectomy*	14	5.5 (1.9, 0.1-32.9)†
	Complete follow-up, benign or stationary indeterminate lesion with no evidence of hormone production	100	28.6 (26.0, 12.1-56.4)
	Normal initial biochemistry, deceased during follow-up‡	14	3.5 (1.6, 0-26.8)
	Normal initial biochemistry, discontinued follow-up	18	6.4 (3.4, 0.1-20.5)
	Regression of lesion§	10	24.0 (21.7, 4.5-36.3)
	Isolated biochemical abnormalities, not operated	4	32.9 (33.2, 24.6-40.7)
	Dead before follow-up¶	27	0
<i>Subtotal</i>		187	18.6
<b>History of extra-adrenal malignancy</b> <i>n=39</i>	Adrenalectomy*	1	0.3†
	Complete follow-up, benign or stationary indeterminate lesion with no evidence of hormone production	26	28.9 (26.5, 13.5-52.2)
	Normal initial biochemistry, deceased during follow-up**	3	17.8 (17.6, 16.2-19.7)
	Normal initial biochemistry, discontinued follow-up	1	0.5
	Isolated radiological abnormalities, not operated	1	23.6
	Dead before follow-up††	7	0
<i>Subtotal</i>		39	21.3
<b>Total</b>		226	19.0

\* For indication and postoperative diagnosis see Table 9. † Time to surgery. ‡ Causes of death: Cardiovascular *n*=5, extra-adrenal malignancy *n*=4, , gastrointestinal *n*=2, psychiatric illness *n*=2, infection *n*=1. § Five cases of traumatic adrenal bleeding and five cases with total regression of lesion on follow-up. || Three patients with elevated cortisol levels after 1 mg-DST, one patient with elevated urinary aldosterone levels, and one patient with a growing indeterminate lesion without evidence of hormone production. ¶ Causes of death: Cardiovascular *n*=13, gastrointestinal *n*=5, extra-adrenal malignancy *n*=3, psychiatric illness *n*=2, infection *n*=2, diabetes type 2 *n*=1, trauma *n*=1. \*\* Causes of death: Extra-adrenal malignancy *n*=2, cardiovascular *n*=1. †† Causes of death: Gastrointestinal *n*=3, extra-adrenal malignancy *n*=2, cardiovascular *n*=2.

No primary adrenal malignancy was found at surgery or during follow-up, and no death occurring before or during follow-up could be attributed to adrenal malignancy. Causes of death were based on autopsies in 14 % of cases.

**Table 9.** Indication for surgery and postoperative diagnosis in all surgically treated patients (n=15), paper II

Group	Indication for surgery	Postoperative diagnosis						Total
		Non-functioning cortical adenoma	Cortisol-secreting cortical adenoma	Aldosterone-secreting cortical adenoma	Juxta-adrenal paraganglioma	Metastasis	Misc.	
<b>Patients with no extra-adrenal malignancy at inclusion</b>	Pheochromocytoma	1*			1†			2
	Primary aldosteronism			3‡				3
	Size+suspicion of autonomous cortisol production		3					3
	Size	2					4§	6
<b>Patients with history of extra-adrenal malignancy</b>	Metastasis					1		1
<i>Total</i>		3	3	3	1	1	4	15

\* High adrenalin levels at two-year follow-up visit and MIBG-scintigraphy concordant with the lesion, postoperative hormone analysis normal. † History and clinical signs of catecholamine production at baseline evaluation. ‡ All had history of hypertension and hypokalemia at baseline evaluation. § One case each of nodular cortical hyperplasia, reactive lymphadenopathy, myelolipoma and post-haemorrhagic cyst.

### **Patient-perceived impacts and Health-Related Quality of Life during diagnosis and follow-up of an AI (paper III)**

111/145 patients (mean age 67 years, 63 % females) responded (response rate 77 %). Data was complete for the AIIQ in 110 cases (109 in items 3 and 8), HADS-A in 108 cases, HADS-D in 109 cases, and SF-36 in 108 cases. For patient characteristics see Table 10.

#### **The Adrenal Incidentaloma Impact Questionnaire**

Exploratory factor analysis supported a two-factor model (eigenvalue > 1) explaining 61 % of the variance. AIIQ items 1, 2, 4, and 5 formed the first factor, labelled preoccupation with the AI, while the second factor, labelled evaluation of the programme as such, comprised items 3 and 6-8. (See Appendix.)

#### *Preoccupation with the AI*

The AI diagnosis caused some worry in 77 % (item 1). During follow-up, 18 % thought about the lesion often (item 2). However, after the follow-up programme only 3 % of the patients reported impacts on their everyday life (item 4), and 14 % thought about the lesion sometimes, while 3 % thought about it often, or all the time (item 5).

**Table 10. Patient characteristics, paper III**

	<b>Responders</b>	<b>Non-responders</b>
<b>Subjects, n (%)</b>	111 (100)	34 (100)
<b>Age, years (mean (median, range))</b>	67 (67, 30-90)	70 (74, 27-89)
<b>Females (n)</b>	70 (63)	20 (59)
<b>HPA axis (mean <math>\pm</math> 2SD)</b>		
UFC at completion (nmol/24 h)	168.8 $\pm$ 201.3	180.7 $\pm$ 143.1
1 mg-DST at completion (nmol/L)	54.7 $\pm$ 63.8	49.6 $\pm$ 43.4
<b>Diagnosis at detection*, n (%)</b>		
B Infection	1 (1)	0 (0)
C Malignant neoplasm	20 (18)	2 (6)
D 00-48 Benign neoplasm	3 (3)	1 (3)
D 50-89 Blood	1 (1)	0 (0)
E Endocrine	1 (1)	0 (0)
F Mental/behavioural	0 (0)	1 (3)
I Circulatory	11 (10)	1 (3)
J Respiratory	4 (4)	2 (6)
K Digestive	36 (32)	11 (32)
M Musculoskeletal	8 (7)	0 (0)
N Genitourinary	2 (2)	2 (6)
R Symptoms	16 (14)	5 (15)
S Trauma	2 (2)	4 (12)
Y External causes	2 (2)	0 (0)
Z Control after therapy	4 (4)	5 (15)
<b>Co-existing conditions, n (%)</b>		
Hypertension	53 (48)	13 (38)
Cardiovascular disease†	25 (23)	6 (18)
Diabetes mellitus	10 (9)	10 (29)
Hyperlipidemia	13 (12)	1 (3)
Osteoporosis	5 (5)	3 (9)
BMI (kg/m <sup>2</sup> ) > 25‡	45 (41)	7 (21)
History of malignancy	18 (16)	6 (18)

\* Result of the work-up for the complaint leading to the radiological examination, grouped in chapters according to ICD-10.

### *Evaluation of the programme*

Only 2 % reported that the termination of follow-up made them feel more worried (item 3). Totally, 10 % reported that their HRQoL was negatively impacted during the follow-up programme (item 6); however only 4 % reported that they experienced the programme as negative (item 7). The majority of patients were satisfied with the information received, but 19 % felt that the information about the adrenal lesion had been insufficient or very insufficient (item 8).



### *Assessment of information*

The patients' assessments of the information given (item 8) correlated with the reaction at termination of the programme (item 3:  $r_s = 0.33$ ), impact on everyday life (item 4:  $r_s = 0.22$ ), preoccupation during last month (item 5:  $r_s = 0.29$ ), and general assessment of the programme afterwards (item 7:  $r_s = 0.30$ ). No differences in the patients' assessments were seen between the participating clinical units.

### **Responses to the Hospital Anxiety and Depression Scale**

In total 12 respondents (11 %) had possible and 19 (18 %) probable anxiety (HADS-A). Sixteen (15 %) had possible and 16 (15 %) probable depression (HADS-D). There was considerable overlap in cases of anxiety and depression with 21 respondents scoring as possible or probable cases of both anxiety and depression. No significant differences were seen between non-cases, possible and probable cases according to HADS with regard to HPA-axis tests (urinary free cortisol levels or 1 mg-DST).

### **Relationships between the AIIQ, HADS and SF-36**

The preoccupation factor correlated to Anxiety (HADS-A,  $r_s = -0.47$ ,  $p < 0.001$ ), and the SF-36 domains Mental Health (MH,  $r_s = 0.73$ ,  $p < 0.001$ ) and Vitality (VT,  $r_s = -0.53$ ,  $p < 0.001$ ). Significant differences were seen between probable cases of anxiety and non-cases (HADS-A > 10 vs. < 8) regarding AIIQ items addressing preoccupation (items 1, 2, 4 and 5,  $p = 0.002$  to  $0.009$ ), with probable cases scoring 0.61-0.85 units lower than non-cases. They also reported a greater impact on HRQoL during follow-up (item 6,  $p = 0.006$ ). However, no differences were seen regarding worry associated with the termination of the programme (item 3). Significant differences were also seen between probable cases of depression and non cases (HADS-D > 10 vs. < 8) regarding impact on everyday life (item 4,  $p = 0.004$ ), thoughts about the AI last month (item 5,  $p = 0.001$ ), and general assessment of the programme after termination (item 7,  $p = 0.02$ ), with probable cases of depression scoring 0.55-0.86 units lower than non-cases.

### ***Surgery for malignant adrenal tumours – the case of adrenal metastases (paper IV)***

Thirty patients with adrenal metastasis (12 female, 18 male, mean (median) age 60.6 (62.5) years, range 30-79 years) were treated and fulfilled the inclusion criteria at our centre during the study period. For patient characteristics and results of the univariate and multivariate analysis see Table 11.

Adrenalectomy for potential cure was achieved in 19 patients (63 %). Median overall survival (95% CI) was 23 (15-31) months, with a 5-year actuarial survival rate of 22.5 %. Median disease-free survival was 6 (0.9-11) months. Three patients were alive with no evidence of disease at 101, 60, and two months of follow-up. Five patients were alive with disease after 120, 52, 34, 24, and 16 months of follow-up. 20 patients died of tumour disease, two of other causes. Independent positive prognostic factors for

survival in the multivariate analysis were adrenalectomy for potential cure, and no previous surgery for metastases. Prolonged survival was seen in patients with metastases from colorectal cancer compared with non-small cell lung cancer. In patients with metachronous metastasis, a disease-free interval > 12 months was associated with a 21 months longer median survival (log-rank test, p=0.03).

**Table 11.** Overall survival according to Kaplan and Meier with respect to 8 different background variables. Univariate and multivariate analysis.

Variable	Mean survival in months (95% CI)	Univariate Analysis (p-value)	Multivariate analysis (p-value)	Hazard ratio
<b>Gender</b>		0.86	n.s.	
male (n=18)	28 (18-39)			
female (n=12)	28 (17-39)			
<b>Tumour type</b>		0.023	0.043	
colorectal cancer (n=4)	42 (27-58)			1.0*
renal cell carcinoma (n=9)	56 (26-85)		0.10*	8.5*
malignant melanoma (n=5)	17 (8-26)		0.13*	6.2*
non-small cell lung cancer (n=5)	12 (4-19)		0.008*	37.6*
other (n=7)	26 (14-38)		0.16*	4.7*
<b>Presentation</b>		0.37	n.s.	
synchronous (n=9)	31 (6-56)			
metachronous (n=21)	40 (23-54)			
<b>Disease-free interval</b>		0.028	n.s.	
metachronous DFI<12 months (n=12)	21 (14-29)			
metachronous DFI>12 months (n=9)	57 (33-82)			
<b>Previous metastasectomy</b>		0.53	0.02	5.8
no (n=20)	42 (23-60)			
yes (n=10)	24 (14-35)			
<b>Size of metastasis</b>		1.00	n.s.	
< 45 mm (n=12)	40 (16-64)			
> 45 mm (n=18)	36 (19-52)			
<b>Surgical technique (OA/LA)</b>		0.14	n.s.	
LA (n=10)	20 (12-28)			
OA (n=20)	46 (26-66)			
<b>Adrenalectomy for potential cure</b>		0.02	0.01	4.9**
yes (n=19)	51 (31-72)			
no (n=11)	14 (9-19)			

OA/LA: Open/Laparoscopic adrenalectomy. \* Versus colorectal carcinoma. \*\*Incomplete resection versus complete resection.

### ***Germ-line mutations in pheochromocytoma/paraganglioma with apparently sporadic presentation (paper V)***

In Western Sweden 256 patients with Pheo or PGL were registered in the NCR (1958-2009) (Figure 13). Of these, 24 had hereditary or syndromic presentation (MEN2 n=13, NF1 n=9, VHL n=1, Carney syndrome n=1), 20 had extra-abdominal PGL, and one patient with primary hyperparathyroidism was misclassified in the register. Information on presentation was missing in 28 deceased patients (Pheo n=6, PGL n=10, malignant Pheo n=9, malignant PGL n=3, mean age 59.2 years, mean time from diagnosis to death 7.6 years). Fifty-six patients were diagnosed post-mortem (Pheo n=39, PGL n=5, malignant Pheo n=12).

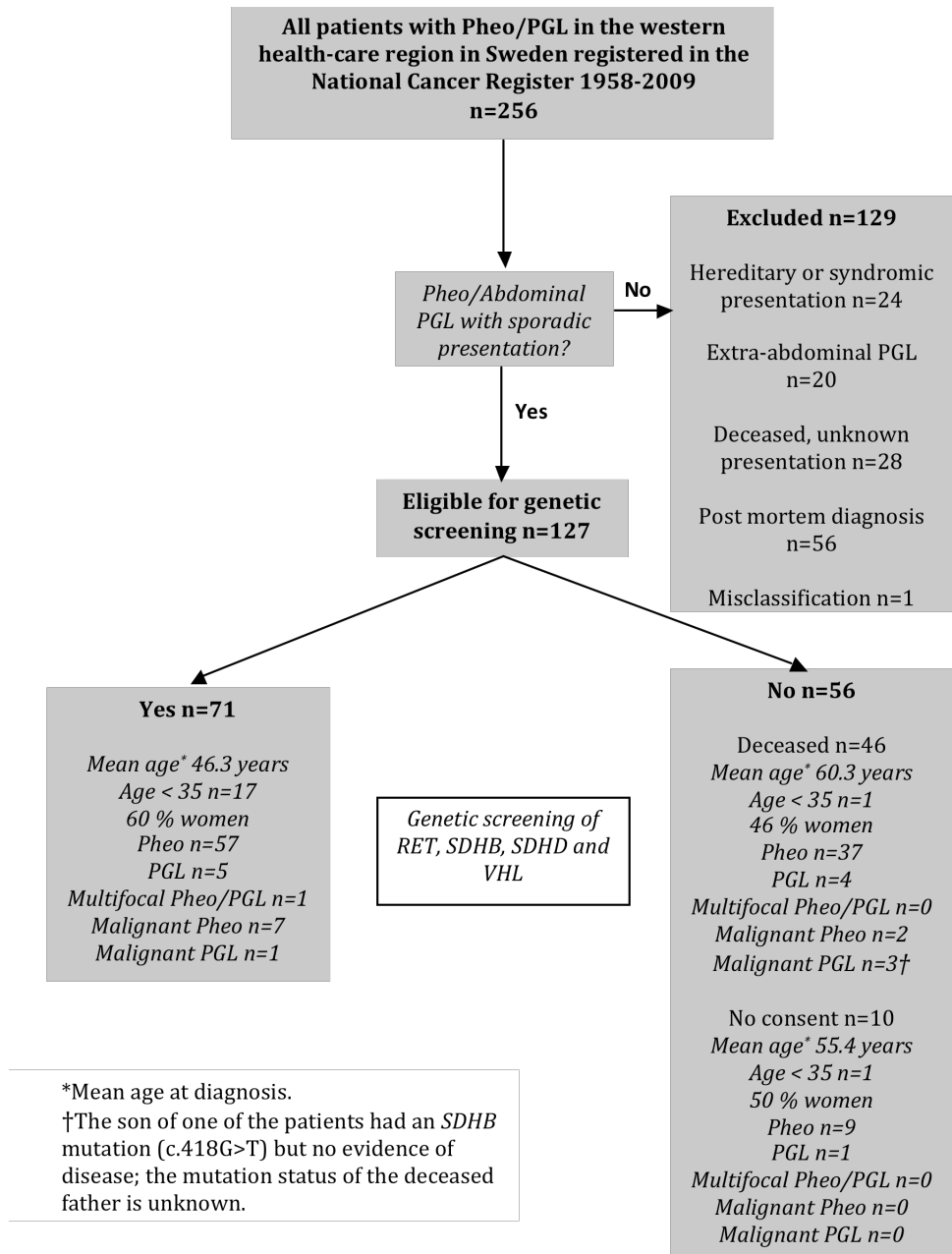
127 patients (mean age 52.5 years, 54 % women) had Pheo or abdominal PGL with sporadic presentation. Of these, 81 were alive and invited to the study, 71 (88 %) gave their consent and underwent testing. Forty-six patients were dead (mean time from diagnosis to death was 12 years).

Sequencing revealed a missense mutation in the *RET*-gene in one patient, and *SDHB*-mutations in three patients (Table 12). Single nucleotide polymorphisms in *SDHB* were present in six patients. No deletions were detected with MLPA analysis. The patient with *RET*-mutation underwent a prophylactic thyroidectomy at age 40, 13 years after surgery for Pheo. No C-cell hyperplasia or medullary thyroid carcinoma was found. All patients with *SDHB*-mutation were alive without evidence of tumour recurrence or malignant development at 15.7, 26.0 and 28.1 years of follow-up, respectively.

**Table 12.** Characteristics of the detected patients with germ-line mutations and sporadic presentation of pheochromocytoma or abdominal paraganglioma

	Patient 1	Patient 2	Patient 3	Patient 4
<i>Age at diagnosis</i>	25	49	15	27
<i>Sex</i>	Female	Male	Female	Female
<i>Diagnosis</i>	Pheo	Pheo	PGL	Pheo
<i>c.DNA</i>	<i>SDHB</i> c.716C>G	<i>SDHB</i> c.725G>A	<i>SDHB</i> c.IVS4+1G>A	<i>RET</i> c.1826G>A
<i>Protein</i>	p.Ser239Cys	p.Arg242His	Splice-site	p.Cys609Tyr
<i>LOVD* ID</i>	Submitted	SDHB_00004	SDHB_00047	/
<i>Follow-up (years)</i>	26.0	15.7	28.1	13
<i>Status at follow-up</i>	NED	NED	NED	NED

None had a malignant, bilateral or multifocal tumour at diagnosis or during follow-up. NED: No evidence of disease. \* Leiden Open Variation Database (168).



**Figure 13.** Patients in Western Sweden with pheochromocytoma or paraganglioma 1958-2009.

## Discussion

### ***Management strategies for patients with AI***

Effective programmes for diagnostic work-up and follow-up require information on the prevalence of AI, and the proportion of malignant and hormone-producing tumours in the intended target population.

### **The prevalence of AI**

In paper I, the frequency of AI at a focused evaluation of abdominal CT scans was 4.5 %, with a wide range (1.8-7.1 %) between hospitals. This is in the upper range of reported prevalence figures at CT (79-82), and approaches the prevalence in autopsy series (Figure 3). These autopsy series include grossly visible lesions down to 2 mm in diameter, compared to radiological series, which generally set a lower size limit at 10 mm (96). The clinical significance of very small lesions may be questioned, but it must be emphasised that aldosteronomas (verified in three patients in paper II) are generally smaller than 20 mm (169). In the study of AI in Western Sweden the smallest verified lesion was 8 mm (Table 7), close to the arbitrary 10 mm threshold.

No difference was seen between patients submitted to the study or patients detected at re-evaluation with regard to lesion size or indication for the examination. Our results suggest a considerable underreporting of AI in clinical practice, as well as in other clinical series.

### **The proportion of malignant and hormone-producing tumours in patients with AI**

During diagnostic work-up and follow-up of patients with AI in Western Sweden (paper II) 6.6 % of patients were operated on suspicion of hormone-producing or malignant tumours, and hormone-producing tumours were verified in 3.1 %. No primary adrenal malignancy was found at detection or during follow-up. All patients with hormone-producing tumours were identified at the first evaluation by an endocrinologist/endocrine surgeon. With the exception of one patient, operated on suspicion of a Pheo based on the 2-year follow-up evaluation (histopathology showed an adrenocortical adenoma), the two-year follow-up did not lead to directed treatment in any case.

The proportion of hormone-producing and malignant tumours in our study (paper II) was lower than in most published series (30, 83, 95, 96). Given that our patients with hormone-producing tumours all were identified at the first evaluation, it is conceivable that even these low figures are an overestimation, should stricter inclusion criteria be applied. The main difference between our study and other published series, including the previous Swedish study (90) was the inclusion mechanism. In the study by Bülow et al. patients were reported from their attending physicians, whereas patients in our

study were included directly from all radiology departments in a defined region. Thus, differences in patient selection offer an explanation for the discrepancies, and the results in paper II probably better reflect the situation in an unselected cohort undergoing radiological examinations.

### **Risk of malignancy developing in an AI over time – value of radiological follow-up**

#### *Radiological follow-up of AI as a method to detect ACC*

ACC is a rare tumour in the population (Table 1) and no ACC was detected during evaluation or follow-up of patients with AI in Western Sweden (paper II). However, in other series the mean reported frequency of ACC in patients with AI was 1.9 - 4.7 % (30, 83, 95, 96). The main purpose of the radiological follow-up in patients with AI is to detect an ACC (86). The underlying argument is that the AI may be an ACC that has been detected by chance at an early stage (stage I), and by close follow-up will be revealed when the disease is still localised (stage I-II), allowing potentially curative surgery.

The validity of this argument for follow-up can be evaluated by the following calculations applied in the screening situation: During the 18 month inclusion period of the Study of Adrenal Incidentaloma in Western Sweden 34044 abdominal CT scans were performed. Assuming a constant rate of examinations, 22696 examinations would have been performed in 2003. With a detection rate of AI of 4.5 % (mean at re-evaluation, paper I), 1021 AI would have been detected. During 2003, three new cases of ACC were registered in the NCR for Western Sweden (42). As only about 50 % of ACCs are non-functioning at detection (36, 170, 171), and 45 % are diagnosed in stage I-II (36, 37, 41) this leaves us with  $3 \times 0.5 \times 0.45 = 0.68$  ACC that could have been incidentally detected stage I ACC, and progressing to a larger stage I, or stage II, tumour at the follow-up examination. The detection rate of localised ACC in patients with AI, using two radiological examinations, would be  $0.68/1021 = 1/1501$ . As standard radiological characterisation detect the majority of malignant tumours at the first examination (120), the true figure for detecting ACC at follow-up is reasonably lower.

If increased use of abdominal imaging had an effect on the detection rate of ACC, it could be manifested by an increased incidence, and/or as an earlier detection with a higher proportion of localised tumours (down-staging). However, the incidence rate of ACC in Sweden has been stationary since 1970 (Table 1). Aso & Homma (172) reported that the number of surgically resected AI in Japan increased more than 10-fold from 1980 to 1988, but the number of ACC during the time period was constant. In a recent publication, Kebebew et al. (37) saw no increase in incidence, or significant trends in the distribution of ACC tumour stages in the US between 1973 and 2000.

#### *Risk of radiation-induced cancer*

The worldwide annual number of diagnostic radiological examinations has more than doubled between 1988 and 2008. In developed countries the annual X-ray frequency between 1997-2007 has been estimated to 1332/1000 inhabitants (173). The Swedish Radiation Protection Agency estimates that the contribution of medical imaging to the total radiation exposure from artificial sources is 80 %, with a theoretical net result of 150-300 new cancer cases per year (174). In a study by Smith-Bindman et al. (175) of 4 hospitals in the San Francisco Bay area the median effective dose of a multiphase CT

scan of the abdomen was 31 milliSievert (mSv) (range 21-43 mSv). It was estimated that with that dose 1/700 women and 1/660 men exposed to a multiphase CT scan of the abdomen at age 60 would develop a radiation-induced cancer. In a sample of dedicated adrenal CTs performed at the Sahlgrenska University Hospital from December 1 2010 to January 31 2011, the effective dose was calculated from the Dose Length Planner using a conversion factor of 0.016 mSv / 1 mGy – cm (176). Seventeen examinations were performed (13 females, 4 males, mean age 60 years). The median effective dose (range) was 18 (6-30) mSv.

Most population-based cancer risk estimates are based primarily on dose-response data of cancer incidence from Japanese atomic bomb survivors (with an average exposure of 0.1 Sv), and the linear no-threshold model, (assuming a dose-response relationship also for low doses of radiation, and an additive effect of repeated exposure (177)). Thus, two adrenal CT scans would result in a similar exposure as a multiphase abdominal CT in the study by Smith-Bindman et al. (175). The linear no-threshold model is endorsed by most regulatory authorities (177), but is not universally accepted (178).

#### *Effectiveness of radiological follow-up in patients with AI*

The effectiveness of radiological follow-up of patients with AI to detect ACC is unproven, and may carry a risk of radiation-induced cancer equal to, or exceeding, the chance of detecting an ACC. Thus, general CT follow-up for AI patients in order to detect ACC cannot be recommended. Subgroups, which may benefit from follow-up, remain to be established.

#### **Risk of hormone-production developing in an AI over time – value of clinical and biochemical follow-up**

In paper II no patient was diagnosed with a hormone-producing tumour during follow-up. In other series the most frequently found hormonal abnormality during follow-up was SH (30, 83, 95, 96). Our study was not designed to focus specifically on SH. In our clinical practice signs of subtle cortisol excess has not been an indication for surgery *per se*, but has strengthened the indications for surgery in patients with otherwise borderline findings (86).

#### *On the definition of SH*

SH is a controversial issue, and there is lack of consensus regarding diagnostic criteria, clinical importance, and optimal management for the condition (179-181). The diagnosis of SH rests on the demonstration of multiple abnormalities in the HPA-axis. As has been pointed out by Cawood (83), multiple testing of HPA-axis function will increase the likelihood of spurious abnormal tests. Thus, the more tests of HPA-axis function that are performed, the higher the prevalence of SH. As most studies use results from additional laborations, rather than a clinical correlate, to confirm the diagnosis of SH, the true sensitivity and specificity of the 1 mg-DST is difficult to validate; the false positive rate even with a high threshold of 140 nmol/l may be up to 30 % (181).

### *Rationale for treatment of SH*

SH has been implicated as a cause of the metabolic syndrome (182, 183), a constellation of cardiovascular risk factors including abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance  $\pm$  glucose intolerance, and a proinflammatory, and prothrombotic state (184). Thus, surgical resection of an adenoma with subtle cortisol-production has been suggested as a means to achieve better metabolic control and reduced cardiovascular risks. In line with the debate on the possible carcinogenic effects of hyperinsulinemia (185), an alternative hypothesis, that the AI may be a result of the metabolic syndrome, mediated by trophic effects of hyperinsulinemia, has been formulated (186). Features of the metabolic syndrome are prevalent among patients with AI. In the Italian series of 1004 patients with AI 92 had SH. Of these 41 % had mild or moderate hypertension, 8 % diabetes, and 38 % obesity. However, only obesity was significantly more prevalent in patients with SH compared to patients with non-functioning tumours (89). Possible bias could be that patients under surveillance, or treatment for other diseases, may be subjected to more radiological examinations (180).

### *Results of surgery for SH*

One small randomised controlled trial on surgery for SH has been published (187). Forty-five patients were enrolled during a 15-year period and randomised to adrenalectomy (n=23) or conservative management (n=22). Three patients in the observation group crossed over to treatment due to an increase in lesion size; all lesions were benign. The only statistically significant difference between the groups was better control of hypertension after surgical treatment. A few retrospective case-control studies (188-190), and small case series (134, 136, 191-194) with varying diagnostic criteria and outcomes have been reported. Recently, in a retrospective analysis of 55 surgically treated patients, Eller-Vainicher et al. (195) reported a sensitivity and specificity of 65.2 % and 68.8 % when a combination of urinary free cortisol  $> 193$  nmol/l, ACTH  $< 2.2$  pmol/l and 1 mg-DST  $> 83$  nmol/l was used to predict the improvement of at least two of the following parameters after surgery: body weight, blood pressure, fasting glucose and LDL cholesterol levels. However, data are not available in the literature on endpoints such as cardiovascular events (stroke, myocardial infarction) or death.

### *Follow-up to detect SH in patients with AI*

It seems evident that some AI have autonomous cortisol secretion. Consensus regarding diagnostic criteria is lacking, which makes the efficacy of treatment difficult to evaluate. At present isolated SH is not an established indication for surgery (86). Randomised trials with validated diagnostic criteria and relevant endpoints are needed to better identify patients that may benefit from treatment of mild hypercortisolism (179), and follow-up to detect SH in patients with AI can be questioned.

### **Patient-perceived impacts of a diagnosis of and follow-up for AI**

Most responders in paper III reported that the diagnosis of AI caused worry, but only 18 % thought about the lesion often during follow-up, and only 4 % experienced the follow-up programme as negative. Still, 10 % reported that the follow-up programme had a negative impact on their HRQoL. An interesting finding was that only 2 % experienced



increased worry after completion of follow-up, indicating that the majority of patients can adjust to the residual uncertainty inherent in being released from surveillance.

Nearly 30 % had possible, or probable, anxiety and/or depression, and these patients also had a more negative experience of the follow-up programme. Co-morbidities were prevalent in the study population, and the frequency of probable and possible cases of anxiety and depression according to HADS was on par with other patient groups with chronic diseases (196-201), and cancer survivors (202, 203).

Personalised and adequate patient information in a follow-up setting after a pathological test result has been shown to reduce anxiety (204). Thus, focused counselling resources to AI patients with a high degree of anxiety at diagnosis may decrease negative psychological effects. However, factors unrelated to the medical intervention are important determinators of the patient-perceived impacts. Bell et al. (205), in a study of psychological adjustment to screening for cervix cancer, found that patients reporting a high degree of initial worry at the abnormal test result were more likely to perceive the information given as inadequate and showed more concern at the time of the interview. Miles & Wardle (206) studied coping strategies and psychological outcomes among participants in a screening programme for colorectal cancer. They found that health-anxious patients were more worried prior to the examination, experienced greater reduction of worry following the examination, but, notably, also less reassurance after screening. van der Steeg et al. (207) found that underlying (state) anxiety was the most significant determinant of HRQoL in women undergoing investigations for a false-positive mammography result. In general, the cognitive process of risk perception and the emotional reaction, or state, of worry are only weakly correlated (208), and patient-associated factors such as educational level (209, 210), living in urban or rural areas (210), number of children (210), and individual coping strategies (206) all correlate with psychological impacts.

An AI can be regarded as a risk factor for having a hormone-producing or malignant adrenal tumour. In counselling an individual patient the concept of risk can be difficult to communicate. Gifford (211) observed that patients and physicians may resolve the problem of risk by interpreting risk factors as illness *per se*. Patient worry about the adrenal lesion has been used as an argument for surgery in patients with AI (212). While individual patient preferences are of great importance in the decision for treatment, the question arises whether surgery, or prolonged follow-up, for a non-functioning radiologically benign adrenal lesion may relieve worry. From the literature on psychological impacts of screening reviewed above, it seems that intervention could relieve worry in a short perspective, but may have limited long-term importance. Data on the psychological effects of surgical intervention is limited.

The retrospective design used in paper III precludes definite conclusions on cause and effect. However, the overall impression is that the follow-up programme was well tolerated, with acceptable impacts on HRQoL. Still, a minority reported adverse effects of the diagnosis and follow-up for AI. Early identification of these patients and focused counselling interventions may be beneficial.

### **Algorithms for diagnostic work-up and follow-up of patients with AI**

Several algorithms for the management of patients with AI have been suggested, *e.g.* (3, 5, 86, 96, 213, 214). In addition to basal clinical evaluation these guidelines rely on repeated biochemical testing and radiological imaging for variable time periods to detect autonomous hormone-production or development of malignancy. Another reason for long-term follow-up for AI proposed by Terzolo et al. (84) is to better control metabolic risk factors and treat associated disease. In contrast to these algorithms, Cawood et al. (83) have argued for a thorough initial work-up to evaluate the risk for malignancy or hormone-production, with repeated radiological imaging after 3 to 6 months reserved for equivocal cases, followed by a decision for either adrenalectomy or discharge without follow-up. With this approach all patients with hormone-producing or malignant tumours identified in paper II would have been identified, and one adrenalectomy performed after the two-year follow-up avoided.

### ***Surgery for adrenal tumours – the case of adrenal metastases***

As seen in paper IV, surgery for adrenal metastases can be performed with low perioperative morbidity, and no perioperative mortality. Median survival was 23 months and in selected patients long-time survival was seen. This is in agreement with other investigators (66, 71, 72, 215). Interpretation of the results of surgery is hampered by the lack of adequate controls, and the multimodal treatment regimes often employed in these selected patients. In paper IV tumour type, and previous surgery for metastasis were identified as independent prognostic factors for survival, and longer survival was seen in patients with metachronous presentation with a long DFI (> 12 months). These and other variables such as size (72) may serve as surrogate markers for underlying tumour biology.

Adrenalectomy for potential cure was also an independent prognosticator for favourable survival. It can be argued that the likelihood to achieve adrenalectomy for potential cure is higher in patients with indolent tumours and limited tumour burden. However, in a small case-control study of patients with non small-cell lung cancer matched for disease extent and performance status, Luketich & Burt (216) saw longer survival in those subjected to chemotherapy and adrenalectomy versus chemotherapy alone (31 versus 8.5 months).

Adrenalectomy for metastasis is feasible, and should be considered in all patients with isolated adrenal metastasis, but also as part of the multimodal management of patients with metastatic disease. Optimal imaging is essential to evaluate adrenal and extra-adrenal tumour burden. Factors such as performance status, tumour type, and presentation must be considered when making a treatment decision.

### ***Prevalence of germ-line mutations in patients with Pheo or abdominal PGL and sporadic presentation in Western Sweden***

The prevalence of germ-line mutations in patients with Pheo or abdominal PGL and sporadic presentation in Western Sweden was 5.6 %. All mutations were seen in *RET* and *SDHB*. *SDHB*-mutations have been associated with malignant Pheo/PGL in 34-37 % (217, 218). Notably, no patient with *SDHB*-mutation in the present series showed evidence of a malignant Pheo/PGL at diagnosis or during follow-up (median 23 years).

The main strength of this study was the well-characterised study population recruited from a prospective population-based register (NCR), also providing some information about patients not tested.

A limitation of our study was that only 71 of 127 patients with Pheo/abdominal PGL and sporadic presentation could be tested, since 56 patients had deceased or did not consent to testing. A further 52 patients had deceased with unknown presentation. It can be argued that the prevalence of germ-line mutations associated with worse prognosis (especially *SDHB*) could be higher in deceased patients. However, when established risk factors for hereditary disease (59, 61) were analysed, tested patients were younger at presentation than non-tested patients with sporadic presentation. The proportion with malignant tumours was slightly higher in the tested group. Also, the reported prevalence of germ-line mutations in patients with solitary benign tumours (87 % of tested patients in Western Sweden) was lower than in patients with multiple or bilateral tumours (59, 60). Immunohistochemical analysis of *SDHB*-expression in tumour tissue (219) is a new method to screen for *SDHx*-mutation carriers, and will provide additional information on mutational status in the deceased patients in our material.

Prevalence figures of germ-line mutations in patients with Pheo/abdominal PGL may differ between study populations based on geographical differences and selection criteria. This must be taken into consideration when formulating screening algorithms for specific target populations.

## Conclusions

- The mean frequency of adrenal incidentalomas at abdominal CT in an unselected population undergoing abdominal CT in Western Sweden was 4.5 %.
- In patients with adrenal incidentaloma (without active extra-adrenal malignancy at detection) 6.6 % were operated on suspicion of malignant or hormone-producing tumours. Hormone-producing tumours were verified in 3.1 %. No primary adrenal malignancy was found. All patients with hormone-producing tumours were diagnosed at baseline examination, and two-year follow-up provided no additional benefit.
- The follow-up programme was well tolerated, and had little impact on everyday life. A minority reported a negative impact of surveillance on their Health-Related Quality of Life. The prevalence of probable anxiety/depression was high in the study population as was the prevalence of concurrent chronic diseases. Probable anxiety or depression was associated with a negative experience of the programme.
- Surgery for adrenal metastases can be performed with no perioperative mortality and low morbidity, and is supported by several prognostic factors. Adrenalectomy should be considered in all patients with isolated adrenal metastases after careful staging, and may also be integrated in the multimodal treatment of patients with disseminated disease.
- The prevalence of germ-line mutations in patients with Pheo/abdominal PGL and sporadic presentation in Western Sweden was 5.6 %, which is lower than in previously reported series.

## Populärvetenskaplig sammanfattning

Binjurarna är två livsviktiga hormonproducerande organ belägna ovan njurarna. Binjurarna består av bark och märg som har olika ursprung och funktion. Binjurebarken producerar kortisol (det kroppsegna kortisonet), aldosteron som är viktigt för saltbalansen och blodtrycket samt vissa könshormoner. Binjuremärgen producerar stresshormonerna adrenalin och noradrenalin.

På grund av den ökande användningen av modern bilddiagnostik (datortomografi, magnetkamera) upptäcks bifynd (förändringar som inte är relaterade till de symptom som föranledde undersökningen) allt oftare. Ett av de vanligaste bifynden vid undersökning av buken är binjuretumörer (så kallade adrenala incidentalom, AI). Binjuretumörer blir vanligare med åldern och ses vid obduktion i upp till 8 % över 70 års ålder. De flesta binjuretumörer är godartade och kräver ingen specifik behandling, men då en del kan vara elakartade (primär eller metastatisk cancer) eller ofysiologiskt hormonproducerande rekommenderas utredning och uppföljning av patienter med AI. Vid fynd av en hormonproducerande eller elakartad tumör kan kirurgisk eller i vissa fall medicinsk behandling vara aktuell.

I denna avhandling har förekomsten av AI hos patienter som genomgått röntgenundersökningar vid alla röntgenavdelningar i Västsverige under en 18-månadersperiod undersökts. Patienter diagnostiserade med AI har genomgått ett standardiserat uppföljningsprogram under två år. Vid misstanke om elakartad eller hormonproducerande tumör värderades patienten för adrenalektomi (borttagande av binjuren), i annat fall avslutades uppföljningen. Effektiviteten av detta program och dess påverkan på deltagarnas livskvalitet har utvärderats. Resultaten av kirurgi för binjuremetastaser (elakartade tumörer i binjurarna som spridits från andra tumörer i kroppen), har också utvärderats hos 30 patienter opererade på Sahlgrenska sjukhuset mellan 1996 och 2007. Dessa tumörer kan upptäckas som bifynd vid röntgenundersökningar, och det har under senare år blivit en vanligare orsak till adrenalektomi. Avslutningsvis undersöktes frekvensen av ärftliga mutationer hos västsvenska patienter som opererats för feokromocytom (binjuremärgstumörer) eller paragangliom (nära besläktade tumörer) registrerade i cancerregistret för Västsverige 1958-2009.

Frekvensen binjuretumörer vid fokuserad granskning av datortomografiundersökningar av buken var 4,5 %. 226 patienter med AI, utan annan känd tumör vid inklusion genomgick ett strukturerat tvåårigt uppföljningsprogram. Av dessa opererades 6,6 % på misstanke om elakartad eller hormonproducerande tumör, och hormonproducerande tumörer hittades hos 3,1 %. Inga elakartade primära binjuretumörer hittades. Alla patienter med hormonproducerande eller elakartade tumörer hittades vid första undersökning i programmet, och ytterligare uppföljning hade inte något värde.

Av 145 patienter som avslutat uppföljning utan tecken på hormonproducerande eller elakartad tumör i november 2007, besvarade 111 (77 %) en utsänd enkät rörande påverkan på livskvalitet av diagnos och uppföljning av AI. Att få besked om ett AI

orsakade oro hos 77 %, och under uppföljningen tänkte 18 % ofta på förändringen. Efter avslutad uppföljning rapporterade endast 3 % att diagnosen och uppföljningen hade påverkat deras livsföring och endast 4 % upplevde att uppföljningsprogrammet hade påverkat livskvaliteten negativt. Att avsluta uppföljningen var associerat med lättnad hos de flesta, endast 2 % upplevde ökad oro. Cirka 30 % hade sannolik ångest eller depression enligt skattningsskalan Hospital Anxiety and Depression Scale, möjligen relaterat till en hög frekvens underliggande kroniska sjukdomar.

Kirurgi för binjuremetastas kunde genomföras med mycket låg komplikationsfrekvens. Medianöverlevnaden efter kirurgi var 23 månader. Positiva faktorer för förlängd överlevnad var radikal kirurgi och inga tecken på tumör på andra ställen, vissa tumörtyper, och ingen tidigare genomgången metastaskirurgi.

Frekvensen ärftliga mutationer var 5.6 % bland 71 patienter som opererats för till synes sporadiskt (ingen känd ärftlighet) feokromocytom/paragangliom.

Sammanfattningsvis gav dessa populationsbaserade undersökningar påtagligt lägre frekvenser av hormonproducerande och maligna tumörer vid AI, och ärftliga mutationer vid feokromocytom/paragangliom än vad som tidigare varit känt. AI var ett vanligt fynd vid skiktröntgenundersökningar av buken. Vid uppföljning av patienter med AI hittades alla hormonproducerande och elakartade tumörer vid den första bedömningen vilket tyder på att uppföljningen kan förenklas avsevärt. Påverkan på livskvaliteten av uppföljningsprogrammet var måttlig, men stödåtgärder för enstaka patienter kan vara motiverat. Positiva prognostiska faktorer för överlevnad efter kirurgi för binjuremetastaser kunde identifieras, och kirurgi bör övervägas hos alla patienter med isolerade metastaser, men även som en del av behandlingen vid spridd sjukdom. Frekvensen av ärftliga mutationer vid feokromocytom/paragangliom i Västsverige var lägre än i tidigare studier. Mutationsfrekvensen har betydelse vid rådgivning och beslut om genetisk testning i denna patientgrupp.

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## Appendix – The Adrenal Incidentaloma Impact Questionnaire, in Swedish

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För några år sedan upptäcktes hos Dig en förändring i binjuren som ett bifynd vid en röntgenundersökning. Denna kontrollerades med blod- och urinprover samt röntgen (datortomografi) vid flera tillfällen innan Du fick besked om att den var ofarlig.

Vi vill gärna veta hur Du upplevde denna situation och är tacksamma för Dina svar på nedanstående frågor även om det gått flera år sedan den upptäcktes. Markera det svarsalternativ som stämmer bäst.

- 1. Beskedet att jag hade en oklar förändring i binjuren gjorde att jag blev**
  - mycket orolig
  - ganska orolig
  - lite orolig
  - inte alls orolig
  - lättad
- 2. Under den period som kontroller pågick tänkte jag på den oklara binjurförändringen**
  - jämt
  - väldigt ofta
  - ibland
  - mycket sällan
  - aldrig
- 3. Efter utredning fick jag besked att förändringen var ofarlig och att ytterligare kontroller ej behövde göras. Detta gjorde att jag blev**
  - mycket lättad
  - lättad
  - varken lättad eller orolig
  - orolig
  - mycket orolig
- 4. Kunskapen om att jag har en binjurförändring har påverkat min livsföring**
  - väldigt mycket
  - mycket
  - lite
  - väldigt lite
  - inte alls
- 5. Under den senaste månaden har jag tänkt på binjurförändringen**
  - jämt
  - väldigt ofta
  - ibland
  - mycket sällan
  - aldrig
- 6. Under utredningsperioden upplevde jag att provtagning och röntgenundersökningar påverkade min livskvalitet**
  - väldigt negativt
  - negativt
  - varken negativt eller positivt
  - positivt
  - väldigt positivt
- 7. Idag upplever jag att få genomgå dessa medicinska undersökningar var**
  - väldigt negativt
  - negativt
  - varken negativt eller positivt
  - positivt
  - väldigt positivt
- 8. Jag tycker sammantaget att informationen om den oklara förändringen har varit**
  - mycket bristfällig
  - bristfällig
  - tillräcklig
  - uttömmande

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