Clinical aspects of Adrenalectomy

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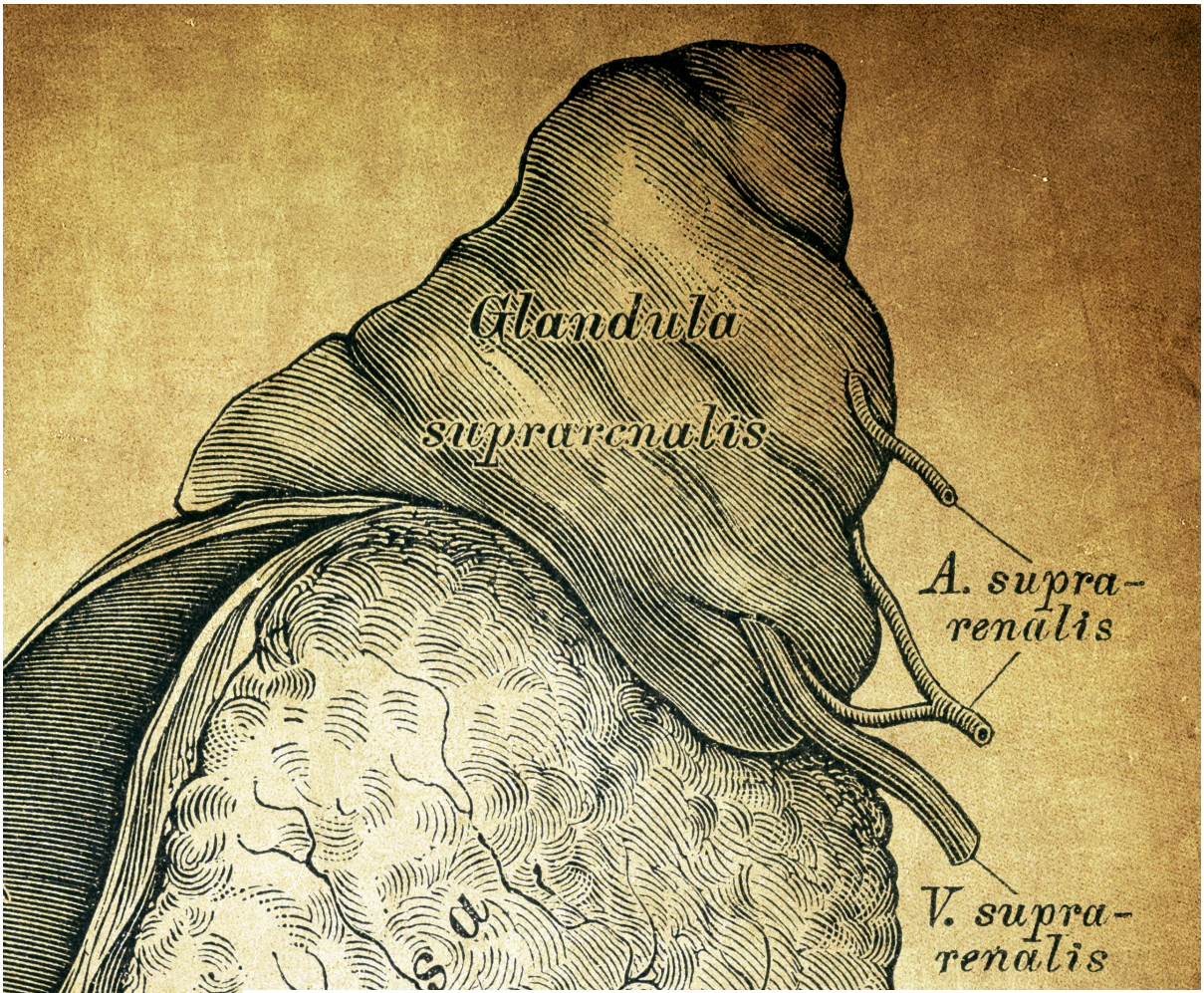

Clinical aspects of Adrenalectomy

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DEPARTMENT OF SURGERY | CLINICAL SCIENCES
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Clinical aspects of adrenalectomy

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LUND
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DOCTORAL DISSERTATION

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DOCTORIAL DISSERTATION

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Abstract
Annual rates of adrenalectomy have doubled in the last 20 years as a consequence of increased detection of adrenal incidentalomas, improved biochemical diagnosis, genetic screening, and minimally invasive surgical techniques. Most adrenal incidentalomas are benign non-functional adrenocortical adenomas. Functional adrenal tumours are associated with high morbidity if left untreated, and this may be the case also for patients with mild hormonal hypersecretion and non-functional adrenocortical adenomas. Malignant tumours may be difficult to diagnose preoperatively, and a significant number of operations are diagnostic procedures. The aim of this thesis was to evaluate the effect and potential value of adrenalectomy, risks of surgery, and health-related quality of life in patients with different adrenal conditions.

Data were derived from the validated national quality register; Scandinavian Quality Register for Thyroid Parathyroid and Adrenal Surgery (SQRTPA) and the European quality register for endocrine surgery, Eurocrine®. For evaluation of health-related quality of life (HRQoL) patients were asked to complete the HRQoL-questionnaire SF-36.

In paper I risk factors for postoperative complications, conversion from endoscopic to open surgery, and hospital stay for more than 3 days were assessed. Complication rate was low and associated with conversion to open surgery. Prolonged hospital stay was associated with bilateral tumour, conversion, open surgery, and hypersecretion of catecholamines. In paper II, HRQoL was evaluated in patients undergoing adrenalectomy. Patients with adrenal tumours reported lower HRQoL compared with a Swedish referent group and HRQoL improved after adrenalectomy in patients with functional tumours. In paper III the impact of adrenalectomy on specific morbidity in patients with mild and clinically overt hypercortisolism and non-functional adrenocortical adenoma were evaluated and compared with age and sex-matched controls. Approximately 50 per cent of the patients with adrenal tumours, regardless of diagnosis, suffered from hypertension preoperatively. Medication for hypertension decreased after adrenalectomy in all patient groups, which was not the case for controls. In paper IV patients registered in Eurocrine® with clinical and subclinical (without symptoms) phaeochromocytomas were studied. Almost half of the patients with phaeochromocytoma undergoing adrenalectomy were incidentally detected and only 88 per cent were diagnosed preoperatively. Among these patients, 91 per cent were treated preoperatively with alpha-blockade. Complication rate was four per cent and did not differ between indications for surgery or patients treated with preoperative alpha-blockade or not.

This thesis shows that adrenalectomy, espcially for patients operated with minimally invasive approach, is a safe procedure with a low rate of surgical complications and rapid recovery regardless of underlying disease. Adrenalectomy has a positive influence on HRQoL in patients with hormonally active adrenal tumours. This thesis also shows that hypertension is common in patients with benign adrenocortical tumour regardless of cortisol secretion. In these patients, adrenalectomy appears to lead to decreased medication for hypertension postoperatively. Complication rate in patients with phaeochromocytoma is not affected by the indication for surgery, and seems not to be higher in patients not treated with preoperative alpha-blockade.

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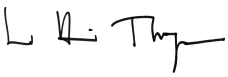
Signature  Date 2021-08-02

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” It always seems impossible until it´s done”

– *Nelson Mandela*

Table of Contents

Original papers

The thesis is based on the following original papers, referred to in the text with their Roman numerals (I-IV):

I. Thompson LH, Nordenström E, Almquist M, Jacobsson H, Bergenfelz A. Risk factors for complications after adrenalectomy: results from a comprehensive national database. *Langenbecks Arch Surg.* 2017; Mar; 402 (2): 315-322.

II. Thompson LH, Nordenström E, Almquist M, Bergenfelz A. Health-related Quality of Life in patients undergoing adrenalectomy: report from a Swedish National Audit. *Langenbecks Arch Surg.* 2019; Nov; 404 (7): 807-814.

III. Thompson LH, Ranstam J, Almquist M, Nordenström E, Bergenfelz A. Impact of adrenalectomy on morbidity in patients with non-functioning adrenal cortical tumours, mild hypercortisolism and Cushing's syndrome as assessed by national and quality registries. *World J Surg.* 2021 June 27. DOI: 10.1007/s00268-021-06214-0

IV. Thompson LH, Makay Ö, Brunaud L, Raffaelli M, Bergenfelz A. Adrenalectomy for incidental and symptomatic phaeochromocytoma: a retrospective multicenter study based on the Eurocrine® database. *Br J Surg.* 2021 July 16. DOI: 10.1093/bjs/znab199

Thesis at a glance

	Study question	Methods	Results	Conclusion
I	Predictive factors for postoperative complications, conversion and length of hospital stay in patients undergoing adrenalectomy	Retrospective study of 659 patients in Sweden registered in SQRTPA 2009-2015	Complication rate was 6.6 per cent and associated with conversion to open surgery. Conversion rate was 7.2 per cent and associated with large- or malignant tumour. Prolonged hospital stay was associated with bilateral tumour, conversion, open surgery and hypersecretion of catecholamines	Minimally invasive adrenalectomy is a safe procedure in most patients with adrenal tumours with low risk for complications, low risk for conversion and short hospital stay
II	Effect of adrenalectomy on HRQoL in patients with functioning, non-functioning and malignant adrenal tumours	Prospective, singel institution study of health related quality of life (HRQoL) in 50 patients undergoing adrenalectomy	Patients with adrenal tumours reported lower HRQoL compared with a Swedish referent group. HRQoL improved after adrenalectomy in patients with functional tumours. There were no improvements in patients with non-functional or malignant tumours	Adrenalectomy has a positive effect on HRQoL in patients with functional adrenal tumours but no effect in patients with hormonally inactive tumours
III	Impact of adrenalectomy on morbidity in patients with mild hypercortisolism	Retrospective study of 271 patients registred in SQRTPA with CS, ACS and non-functioning adrenocortical adenoma compared with age- and sex matched controls	Approximately 50 per cent of patients in all tumour groups suffered from hypertension. The use of antihypertensive dugs decreased after adrenalectomy in patients but not in controls	Hypertension is more common in patients with benign adrenal tumour regardless of cortisol secretion compared with controls. Adrenalectomy seems to have a positive effect on hypertension in these patients
IV	Differences in the clinical presentation and operative outcome in patients with asymptomatic- and symptomatic phaeochromocytoma	Retrospective, European study of 551 patients with phaeochromocyto ma registered in Eurocrine® undergoing adrenalectomy 2015-2020	Some 43 per cent of the phaeochromocytomas were detected as incidentalomas and 12 per cent were only diagnosed after surgery on histopathology. The rate of complications was four per cent and did not differ due to indication for surgery or in patients with or without preoperative alpha-blockade	Subclinical phaeochromocytoma is common and often present as an incidentaloma. A significant proportion of patients with phaeochromocytoma are not treated with preoperative alpha-blockade, seemingly without negative effects on surgical complications

Abbreviations

AI	Adrenal incidentaloma
ACC	Adrenocorticalcancer
ACS	Autonomous cortisol secretion
ACTH	Adrenocorticotropic hormone
ARR	Aldosterone/renin ratio
ATC	Anatomical Therapeutic Chemical code
COMT	Catechol-O-methyltransferase
CRH	Corticotropine releasing hormone
CS	Cushing´s syndrome
CT	Computed Tomography
DDD	Defined daily dose
DHEAS	Dehydroepiandrosterone sulphate
^{18}FDG	18F-fluoro-2-deoxy-D-glucose
FDOPA	Fluorodopa
^{68}Ga	Gallium 68
GEP-NET	Gastroenteropancreatic neuroendocrine tumours
HRQoL	Health Related Quality of Life
HU	Hounsfield units
ICD-10-SE	International classification of diseases 10th version
LOS	Length of stay
MAO	Monoamine oxidase
MEN2	Multiple endocrine neoplasia type 2
MID	Minimally important difference
MRI	Magnetic Resonance Imaging
NFAA	Non-functioning adrenocortical adrenoma
NPR	The National Patienr Register
PA	Primary aldosteronism
PET	Poisson emission tomography
PIN	Personal identity number
PROMS	Patient reported outcome measures
RAAS	Renin-angiotensin-aldosterone-system
SDHB	Succinate dehydrogenase B
SF-36	36-item short form health survey
SPDR	The Swedish Prescribed Drug Register
SQRTPA	Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal surgery

Introduction

Adrenal tumours are fairly common. Most adrenal tumours do not cause overt disease and after initial investigation requires no surgical treatment or follow-up. However, some tumours may be life-threatening if not detected and treated in due time.

Adrenal incidentaloma (AI) is defined as an adrenal tumour detected incidentally on imaging performed for other reasons than suspected adrenal disease. Further investigation is therefore warranted to determine if the adrenal tumour is malignant or benign and hormonally active or not. Adrenal incidentalomas are detected in approximately one to four per cent of abdominal imaging and are more common in older age[1, 2].

Adrenal surgery has become more frequent as a consequence of AI, diagnosis of hormonally active tumours in patients with hypertension, screening of adrenal tumours in patients with hereditary syndromes, and minimally invasive surgical techniques[3]. Multidisciplinary evaluation and care are required due to diagnostic challenges and the broad spectrum of disease. Adrenal tumours with hormonal hypersecretion are often treated with adrenalectomy. The secretion of adrenal hormones may vary and cause clinically obvious disease or subclinical disease, despite causing quite a similar morbidity. For instance, it is unclear if patients with mild hypercortisolism benefit from adrenalectomy and the wider management of these patients have not been clarified.

Some patients are treated with adrenalectomy without clear evidence for effect on morbidity, most often because of the size of the tumour, tumour growth, patient preference, or subclinical disease. Thus, health-related quality of life (HRQoL) is an important outcome measure in adrenal surgery. Risks and benefits of adrenal surgery, including surgical techniques, need to be further evaluated to improve clinical practice for patients with adrenal tumours.

The aims of this thesis were to study clinical aspects of adrenalectomy for patients with adrenal disease with a focus on complications, HRQoL, and treatment of patients with subclinical disease, especially regarding morbidity.

Background

Anatomy and physiology

The adrenal glands, *glandula suprarenale*, are located in the retroperitoneum above the kidneys. They develop from two separate embryological tissues: the inner *medulla* origins from neural crest cells and as discovered lately from Schwann cell precursors. The surrounding *cortex* is developed from the intermediate mesoderm[4]. The adrenal gland weights approximately 3.5 grams but, despite its small size, the adrenal gland secretes vital hormones. The adrenal medulla is the main hormonal component of the autonomic nervous system and produces *catecholamines* (adrenaline, noradrenaline and dopamine) when it is activated by the sympathetic nervous system. The adrenal cortex is divided in three zones; zona glomerulosa produces *mineralocorticoids* (aldosterone), zona fasciculata produces *glucocorticoids* (cortisol) and zona reticularis produces *androgens*.

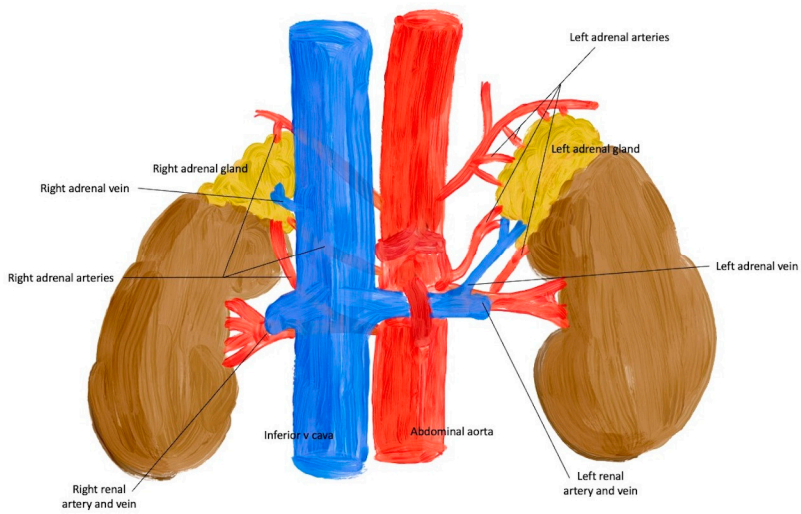

Figure 1
Anatomy of the adrenal glands. Illustration by author

Aldosterone is important for the regulation of blood pressure. It is part of the renin-angiotensin-aldosterone-system (RAAS) and induces reabsorption of sodium and water and excretion of potassium in the renal tubules. Hypersecretion of aldosterone increases the blood volume, whereby perfusion of the juxtaglomerular apparatus increases and inhibits renin production in the glomeruli.

Cortisol release is stimulated by adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH in turn responds to corticotropin-releasing hormone (CRH) from the hypothalamus. This is called the hypothalamic-pituitary-adrenal axis. Cortisol is normally released in a diurnal cycle and inhibits the secretion of ACTH. Stress and low blood-glucose levels increase hormonal secretion to facilitate the release of energy stores and thus raise plasma glucose levels for utilization during stress. Another important function is the suppression of the immune system.

Catecholamines are produced continuously and in response to stress. Catecholamines affect the degree of alertness and increase blood pressure and heart rate. The half-life of circulating catecholamines is only a few minutes and they are degraded by monoamine oxidases (MAO) and catechol-O-methyltransferases (COMT). The metabolites methoxy-adrenaline and methoxy-noradrenaline diffuse continuously from the gland independent of the secretory release.

The adrenals secrete a variety of *androgens* with low androgenic activity, for instance, dehydroepiandrosterone sulfate (DHEAS), which are circulating precursors for peripheral conversion to hormones such as testosterone and estradiol.

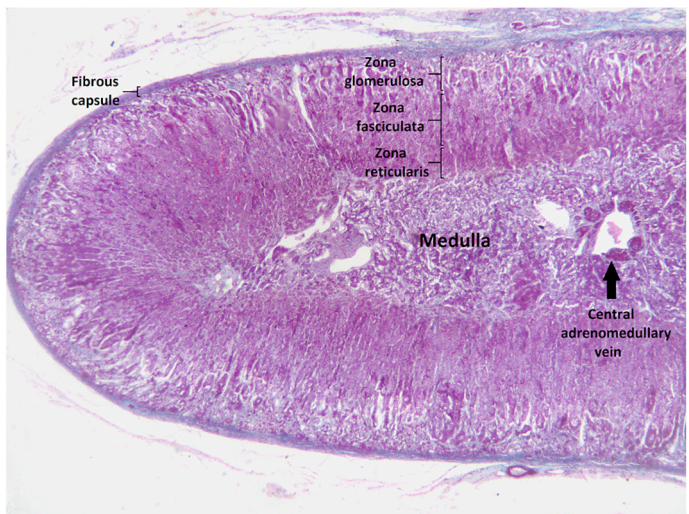

Figure 2
Adrenal gland - histology

The adrenal glands are highly vascularized. The blood supply derives from a myriad of arterioles originating from three small adrenal arteries, superior-, middle-, and inferior adrenal arteries, which creates a network of arterioles within the gland. The gland is drained through the adrenal veins: the right adrenal vein drains into the inferior vena cava and the left adrenal vein drains into the left renal vein.

Adrenal tumours

Incidentaloma

Adrenal incidentalomas (AI) are defined as adrenal tumours detected on imaging performed for indications other than suspected adrenal disease. The final diagnosis may be benign or malignant- and with or without hormonal hypersecretion. The prevalence of AI in autopsy studies is roughly two per cent[5, 6]. Imaging studies suggest a prevalence of approximately one to four per cent, but with an increased prevalence with older age[1, 2]. The detection of AI has escalated over the last years due to several factors including improvements in imaging techniques, increased availability of computer tomography (CT) and magnetic resonance imaging (MRI) and more widespread use of imaging in an ageing population.

The investigation of an adrenal incidentaloma is focused on excluding malignant disease or treatable functional tumours. The underlying tumour types in AI is presented in Table 1.

Table 1
Adrenal incidentalomas. Underlying tumour types. Aggregated data from multiple studies[7]

Tumour type	Median frequency in clinical studies, % (range)	Median frequency in surgical studies, % (range)
Adrenal adenoma	80 (33-96)	55 (49-69)
Non-functioning adrenal adenoma	75 (71-84)	69 (52-75)
Cortisol-secreting adenoma	12 (1-29)	10 (1.0-15)
Aldosterone-secreting adenoma	2.5 (1.6-3.3)	6 (2.0-7.0)
Phaeochromocytoma	7 (1.5-14)	10 (11-23)
Adrenocortical carcinoma	8 (1.2-11)	11 (1.2-12)
Metastasis	5 (0-18)	7 (0-21)
Other benign tumours	-	17

Considerations in adrenal incidentalomas

A benign adrenal cortical adenoma is the most prevalent finding in AI. With available diagnostic methods, malignant tumours may be difficult to diagnose. The preferred surgical technique for adrenal tumours is minimally invasive surgery. Malignant or large

tumours are often treated with open adrenalectomy. Indication for surgical treatment of some adrenal adenomas with mild hormonal hypersecretion has not yet been established. Small, benign non-functioning adrenal tumours are usually not treated with surgery.

Patients with AI are managed by national and international guidelines as shown in the flowchart (Fig 3)[7].

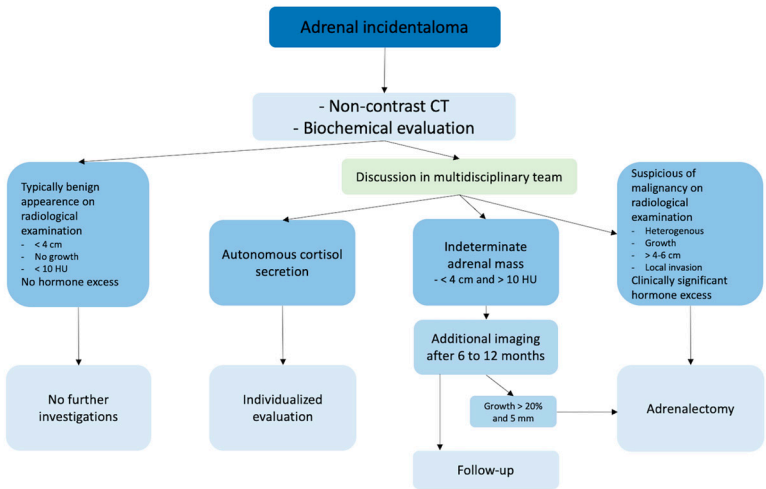

Figure 3
Flowchart on the management of patients with adrenal incidentalomas[7]

Hypercortisolism

Cushing´s syndrome

Hypercortisolism may present with mild or severe symptoms. Cushing´s syndrome (CS) is caused by prolonged exposure to high cortisol levels. Among several pathogenetic mechanisms for endogenous CS the most common forms are: ACTH-overproduction from a pituitary adenoma, also called Cushing´s disease (50-70 per cent), autonomous cortisol producing adrenal cortical adenoma (20-30 per cent) and ectopic ACTH-producing tumours (5-25 per cent), due to, for instance, small-cell lung carcinoma and neuroendocrine pancreatic tumours[8-10]. Some other reasons for CS include cortisol producing adrenocortical cancer and adrenal cortical hyperplasia.

Prolonged supraphysiologic treatment with glucocorticoids is known as iatrogenic Cushing's syndrome. Hypersecretion of cortisol may also occur in major depressive disorder, severe obesity and alcoholism, i.e., pseudo Cushing´s syndrome[8].

Endogenous CS is a rare endocrine disorder with an annual incidence of 2.3-3.2 patients per million[9, 11]. Cushing´s syndrome is at least three times more prevalent in women compared with men and the patient age is usually 20-70 years at detection[8-11].

Overt CS is a severe disease associated with multiple comorbidities, impaired quality of life and increased mortality if left untreated. Cardiovascular disease and infections are the most frequent causes of death [10, 12].

Clinical complications and comorbidities include hypertension, obesity, impairment of glucose tolerance, dyslipidaemia, osteoporosis, decreased cognitive functions, depression or mania, impairment of sexual function, increased risk of infection and dermatological manifestations, such as skin thinning and bruises[13].

Surgical removal of the affected adrenal gland or pituitary is the first-line treatment to normalize cortisol secretion. Ectopic ACTH producing tumours are managed oncologically, which may include surgical excision of the tumour or in specific circumstances bilateral adrenalectomy.

Autonomous cortisol secretion

Patients with biochemical evidence of cortisol hypersecretion without clinical signs of Cushing´s syndrome are referred to as subclinical Cushing´s syndrome, subclinical hypercortisolism or more recently as autonomous cortisol secretion (ACS). Among adrenal incidentalomas, ACS is present in 5-30 per cent of the tumours, depending on diagnostic criteria[14, 15]. Patients with ACS rarely progress to overt CS[16, 17]. Patients with ACS have an increased risk of hypertension, hyperlipidaemia, glucose intolerance and osteoporosis quite similar to patients with CS[18-21].

Current guidelines recommend screening for hypertension, diabetes mellitus type 2 and vertebral fractures in patients with ACS, but the role of adrenalectomy in patients with ACS is unclear[7].

Diagnosis of hypercortisolism

The diagnosis of CS is based on clinical evaluation, laboratory tests and anatomical imaging. The basic screening test recommended for cortisol excess is a 1-mg overnight dexamethasone suppression test.

There is no globally accepted consensus on the definition of ACS. Guidelines suggest that without clinical signs of CS, cortisol levels <51 nmol/L after dexamethasone suppression test excludes cortisol excess. Levels 51-138 nmol/L represent possible ACS and >138 nmol/L definitive ACS[7].

Additional laboratory tests include diurnal variation of plasma or saliva cortisol concentration, 24-hour urine cortisol excretion and plasma ACTH.

Primary aldosteronism

Patients with primary aldosteronism (PA) have autonomous hypersecretion of aldosterone from one or both of the adrenal glands which lead to reabsorption of sodium and water and excretion of potassium. Primary aldosteronism results in hypertension and in approximately half of the patients hypokalemia. Primary aldosteronism is a frequently overlooked cause of hypertension with a prevalence among hypertensive patients estimated at 5 to >10 per cent[22, 23]. The most common causes for PA are bilateral adrenal hyperplasia (60-65 per cent) and unilateral adrenal adenoma (30-35 per cent)[24]. Some other causes include unilateral adrenal hyperplasia (2-3 per cent) and in rare cases adrenocortical cancer or familiar hyperaldosteronism. Primary aldosteronism caused by adrenal adenoma is known as Conn´s disease, named after the medical endocrinologist who first described the disorder in 1955[25].

Hypertension in PA is associated with an increased risk for cardiovascular and renal morbidity compared with essential hypertension[26, 27].

Bilateral disease is treated medically with aldosterone antagonists, whereas surgical resection is generally accepted as the standard treatment in unilateral disease[28, 29].

Surgical or medical treatment lower blood pressure, resolve hypokalaemia and reduce medication for hypertension[22].

Diagnosis of primary aldosteronism

Since PA is common and associated with high morbidity, screening is recommended in patients with persistent hypertension despite three antihypertensive drugs, hypokalaemia, young age and a first-degree relative with early-onset hypertension or cerebrovascular accident[22]. The aldosterone/renin ratio (ARR) is the initial diagnostic method to detect PA. To establish or exclude PA one or more confirmatory tests are recommended, for instance, oral sodium loading test, saline infusion test, captopril challenge test and fludrocortisone suppression test. Adrenal venous sampling

is used to differentiate between unilateral or bilateral disease, especially in older patients with equivocal results on CT.

Phaeochromocytoma

Phaeochromocytomas are neuroendocrine tumours arising from chromaffin cells in the adrenal medulla. Phaeochromocytomas produce and release an excess of catecholamines and metabolites which amplify the activity of the sympathetic nervous system. Symptoms may include headache (related to hypertension), tachycardia and diaphoresis. Some other common signs and symptoms are tremor, nausea, anxiety and hyperglycaemia.

The secretion and release of catecholamines are variable: continuous secretion results in constantly increased levels of circulating hormones and a paroxysmal secretion due to overload of catecholamines in the sympathetic nerves, which in turn are released by stimuli such as pain, stress and tumour compression[30]. The clinical presentation is influenced by the magnitude and type of catecholamines that are secreted, the pattern of secretion, the rate of degradation of the hormones and individual sensitivity to catecholamines[31, 32].

Phaeochromocytoma is a rare disorder but autopsy studies have indicated that a significant proportion of tumours (0.05 per cent) remain undiagnosed during life[33]. This is in agreement with recent studies which report that phaeochromocytoma occurs in four to seven per cent among patients with incidentaloma[7, 34].

For many years phaeochromocytoma was referred to as the "ten-per cent tumour" reflecting approximately ten per cent bilateral tumours, ten per cent malignant, ten per cent extra-adrenal and ten per cent familial. Recent reports indicate that genetic mutations are present in approximately 60 per cent of phaeochromocytomas and paragangliomas, of which 2/3 are germ-line- and 1/3 somatic mutations[35-37]. Consequently, genetic testing is indicated in all patients with phaeochromocytoma[38]. Phaeochromocytomas are included in some familiar syndromes, for instance, multiple endocrine neoplasia type 2 (MEN 2), Von Hippel Lindau syndrome, Neurofibromatosis type 1 and mutation in succinate dehydrogenase genes (SDH). Bilateral tumours are more often encountered in patients with a genetic predisposition.

Adrenalectomy, which is the only curative treatment for phaeochromocytoma, was historically associated with high mortality related to perioperative cardiovascular complications. Preoperative treatment with alpha-adrenergic blockade has therefore been recommended to prevent hemodynamic instability and severe and even lethal cardiovascular events[38]. Improvements in anaesthetic methods and the use of

minimally invasive surgery with less trauma due to less traction, pushing and pressure during surgery, may lead to a re-evaluation of these guidelines[39, 40].

Diagnosis of phaeochromocytoma

To exclude phaeochromocytoma measurement of plasma free metanephrines or urinary fractionated metanephrines is recommended[38]. For anatomical imaging preferably non-contrast CT, and MRI is used. Recent advances in genetic understanding and molecular imaging propose an individualized approach depending on genotype, clinical presentation and anatomical location[41]. Specific available methods are ^{18}FDG-, ^{18}FDOPA- and ^{68}Ga-DOTATATE-PET[42].

Non-functioning adrenal adenoma

The most frequent pathological finding in adrenal incidentaloma is adrenal cortical adenoma (80 per cent of AIs). The majority of these benign tumours, approximately 90 per cent, are not associated with clinically relevant hormonal hypersecretion [6, 43]. The tumours are hence referred to as non-functioning adrenocortical adenomas. Although patients with non-functioning adrenocortical adenomas show no clinical or laboratory signs of hormonal excess, it has been reported that these patients have an increased risk of metabolic syndrome, diabetes mellitus and hypertension[44-47]. Most studies agree that non-functioning adrenocortical adenoma and ACS rarely progress to CS[16, 48]. However, one study found that 31 per cent of patients with non-functioning adrenocortical adenoma developed ACS[49]. It has been hypothesized that non-functioning adrenocortical adenomas may secrete a slight excess of hormones albeit not detectable with standard diagnostic methods[44, 50]. The role of adrenalectomy in patients with non-functioning adrenocortical adenoma has not been investigated. Current guidelines do not recommend follow up or adrenalectomy in patients with small, non-functioning adrenal tumours unless clinical signs of endocrine activity develop[7].

Malignant tumours of the adrenals

Adrenocortical carcinoma

Adrenocortical carcinoma (ACC) is a rare highly malignant tumour with an annual incidence of 0.5-2 per million[51]. The average age at presentation is 50-60 years[52]. The prognosis of ACC is poor, with a median overall survival of about three years from diagnosis, depending on tumour stage at detection, hormonal excess and tumour

resection margins[51, 53]. Most ACCs are sporadic tumours. A small proportion are hereditary tumours mainly in the paediatric population[54].

Clinical presentation is variable with more than 15 per cent detected as adrenal incidentalomas[55]. Possible symptoms include those related to hormonal excess, especially cortisol or a mixed presentation of hormones (androgens or catecholamines), local compression by a large mass and cachexia[56, 57].

Adrenocortical carcinoma is treated with microscopically marigin-free resection, *en bloc* resection including the periadrenal fat and if necessary multi-visceral resection and lymphadenectomy with complete resection of the tumour in combination with adjuvant chemotherapy and mitotane[57]. Despite this aggressive treatment, the rate of recurrence is high[51].

Malignant phaeochromocytoma

Only approximately ten per cent of phaeochromocytomas are malignant[58]. There are no reliable histological features to distinguish benign from malignant phaeochromocytoma. Recently the previous classification system of benign and malignant phaeochromocytoma was replaced by the World Health Organization (WHO) classification of 2017[59]. All phaeochromocytomas are considered to have metastatic potential. The presence of chromaffin tissue at sites distant from the primary tumour (metastasis) is the only certain evidence of malignant phaeochromocytoma[51]. Some hereditary forms have been identified with a higher malignant potential, e.g. SDHB (succinate dehydrogenase B) mutations[36].

Metastasis

Metastases of other tumours are the most frequent malignant tumours of the adrenal glands. Common primary sites are kidney, lung, colon, stomach, oesophagus, liver and pancreas[60]. Other possible malignancies include thyroid, breast and melanoma.

Adrenalectomy for metastases is usually performed after treatment of the primary tumour. These patients should always be discussed at a multidisciplinary tumour conference.

Diagnosis of malignant tumours

To exclude or prove malignant adrenal tumours non-contrast CT and biochemical evaluations are performed in all adrenal masses.

If a malignant adrenal tumour is suspected, a thoracoabdominal contrast-CT and ^{18}FDG-PET is recommended to detect any non-adrenal primary tumour and metastases[57].

Diagnostic challenges

Malignant disease

Non-contrast CT plays an essential role in the anatomic evaluation of AI. Benign tumour characteristics are tumour homogeneity, attenuation <10 Hounsfield units (HU) and small size (<4 cm). MRI and ^{18}FDG-PET are effective in the diagnosis of benign or malignant adrenal tumours. In contrast, heterogenous tumours, large tumours or tumours with HU >10 are not unequivocally malignant disease[61]. In patients with an indeterminate adrenal mass on CT, further imaging modalities may be considered and repeated CT with intervals for possible tumour growth, is recommended[7].

An adrenal biopsy is usually contraindicated[51]. Biopsy of a curable ACC constitutes a risk for tumour dissemination and may trigger hypertensive crises in an undiagnosed phaeochromocytoma. Morphologically it may even prove difficult to differentiate adrenal cortical adenoma from carcinoma on final histopathology[51]. To exclude or prove a diagnosis of adrenal metastasis, a preoperative biopsy might be indicated in specific situations[51].

These diagnostic difficulties infer that many patients undergo adrenalectomy as a diagnostic procedure to exclude a malignant tumour, although ACC is very rare.

Biochemical difficulties for differential diagnosis

The hormonal evaluation may provide other challenges. Secretion of different hormones is influenced by the circadian rhythm, age, sex and a variety of drugs[7].

Adrenal surgery

History of adrenal surgery

In 1552 Bartolomeus Eustachius, an Italian anatomist was the first to recognize the adrenal glands as an anatomical entity[62]. Only 100 years later Thomas Wharton showed an association between the nervous system and the excretion of substances to the circulation. In the late 19th century diseases related to hormonal excess and deficiency postoperatively were described.

The first documented successful adrenalectomy was carried out by Dr Knowsley Thornton in 1889. He removed a 9 kg adrenal tumour from a 36-year old woman

through a T-shaped subcostal incision[63]. The patient died two years later, likely from adrenocortical carcinoma.

Initially, the postoperative mortality was high, 30-50 per cent. Although the clinical features of Addison´s disease were documented, the disease was not universally accepted for many years. William Osler was the first to extract cells from the adrenal gland from pigs to treat adrenal insufficiency. Synthesis of cortisone was discovered in 1940 and the first successful series of adrenalectomies for Cushing´s syndrome was described at the Mayo Clinic in 1949. There were no deaths in the group of patients treated with cortisone replacement.

The discovery of aldosterone in 1953 and primary aldosteronism in 1955 led to an opportunity to surgically treat some patients with hypertension. However, it was shown that PA accounted for only a small proportion of hypertension- albeit more accurate biochemical testing has led to a revival in the interest for the disease.

The first successful adrenalectomy for phaeochromocytoma was carried out by Cesar Roux in Lausanne, in 1926. For many years adrenalectomy for phaeochromocytoma carried high mortality, mainly related to uncontrolled pre- and perioperative hypertension. In 1956 new anaesthetic methods to improve blood pressure control was introduced, which led to safer surgery with almost zero mortality.

The choice of incision in open adrenalectomy varies depending on pathology, tumour site and size. Anterior incision enables bilateral exploration and resection of large tumours. A lateral incision allows great access in the case of unilateral pathology. Retroperitoneal incision avoids the abdominal cavity and allows bilateral exploration but is inadequate for larger lesions.

In 1992 Gagner et al first described laparoscopic adrenalectomy in three patients, two patients with Cushing´s syndrome and one patient with phaeochromocytoma, respectively[64].

Advantages of different surgical techniques

Since the first adrenalectomy performed with a minimally invasive technique, several studies have compared laparoscopic adrenalectomy with open adrenalectomy. The results are consistent with less postoperative pain, shorter hospital stay, lower estimated blood loss, good cosmetic result and generally decreased morbidity[65, 66]. Laparoscopic adrenalectomy is hence considered the standard of care for most patients with adrenal tumours[67, 68].

The anatomic location of the adrenal glands has led to the development of several minimally invasive endoscopic techniques such as transabdominal laparoscopic-, posterior retroperitoneal- and transabdominal robotic-assisted techniques as the most common. All techniques come with different merits and problems.

Transabdominal laparoscopic adrenalectomy is available at most surgical departments. The surgeon has access to a wide working space due to the insufflation of carbon dioxide and can easily recognize conventional anatomic landmarks.

In *posterior retroperitoneal adrenalectomy,* the retroperitoneal working space is fairly small, and the visualisation of anatomical structures is unfamiliar to most general surgeons and the approach is mostly used for small tumours. The technique has been described as superior or comparable with laparoscopic adrenalectomy for operative time, complications and recovery[69]. However, a greater rate for capsular rupture has been described as has postoperative neuralgia and relaxation of the abdominal wall[70, 71].

Robotic-assisted adrenalectomy may be performed transabdominally or retroperitoneally. The technique has been criticised for its long operation time and high costs[69]. Recent reports indicate that benefits and perioperative outcomes are similar to laparoscopic adrenalectomy[72, 73]. The robotic-assisted technique may provide advantages for partial resection of the adrenal and surgery for large tumours especially in obese patients[74]. Without question, the robotic-assisted technique provides superior ergonomics for the surgeon.

Adrenalectomy in large tumours

Laparoscopic adrenalectomy for tumours with suspected malignancy and tumours larger than 6 cm is controversial[75]. Surgery for ACC should include *en bloc* resection with negative surgical margins and without capsular rupture. Since this is of crucial concern for the prognosis in ACC, open adrenalectomy is recommended when ACC is confirmed or highly suspected on imaging[57]. There is no exact cut-off value for size to recommend for open surgery. Recent studies report advances in surgical outcome for robot-assisted adrenalectomy in larger tumours. Equivalent oncological outcome in patients with ACC smaller than 10 cm has been suggested, regardless of open- or laparoscopic adrenalectomy provided that the procedure is performed by an experienced surgeon[76].

Endocrine surgical registers

SQRTPA

Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal surgery (SQRTPA, www.sqrtpa.se) was launched in 2004[77]. Adrenal surgical procedures have been included in the register since 2009. The database is open to all surgical departments within Scandinavia and is recognized by the Swedish National Board of Health and Welfare as the national quality registry within the field. The Swedish Society of Endocrine Surgery recommends participation in the register. Currently, seven surgical departments in Sweden report adrenalectomies to SQRTPA. The coverage is validated against The National Patient Registry annually. Register data are validated annually by an external audit with random visits to participating departments.

The individual hospital responsible for the diagnosis and treatment of the patients reports data directly to the online database at the time of surgery. Follow-up is performed after approximately six weeks and at six months.

Eurocrine®

Eurocrine® is a European surgical quality register of endocrine surgical procedures[78]. The database was initiated in 2015 with a grant from the Health Program of the European Union but is currently run by the *not-for-profit* Eurocrine Society- with seat in Vienna.

The register collects data on surgically treated tumours in the thyroid, parathyroid, adrenal glands and gastroenteropancreatic neuroendocrine tumours (GEP-NET). The register aims to decrease morbidity and mortality by raising clinical standards and reduce differences between clinics and countries. It also aims to provide data for clinical research purposes. The database is ideal for prospective clinical trials. Currently, data on adrenalectomies are registered at 48 departments in 11 countries.

The individual hospital is responsible for entering the data in the online database at the time of surgery and follow-up. SQRTPA has been integrated with the Eurocrine® platform and mandatory core-variables are identical among the two registers. Additional variables may be added on a national level but also for the individual department. Collected data is stored globally with a pseudo-identification number (ID). Mapping between patient-ID and pseudo-ID is kept locally in each department.

National registers of The National Board of Health and Welfare

The National Board of Health and Welfare administrate national registers to facilitate analyses and development of Swedish health care and social services[79]. Quality and validity checks of data are performed regularly. The registers are based on the Swedish personal identity number (PIN) as a unique identifier[80]. The PIN is used in routine health care and medical research, as a link between medical and national registers.

The National Patient Register

From 1987 the Swedish National Patient Register (NPR) includes all in-patient treatment episodes in Swedish hospitals. The register records data on the patients' sex, age, PIN, the dates of hospitalizations, discharge diagnoses, and surgical procedures.

The Swedish Prescribed Drug Register

Since 2005 the Swedish Prescribed Drug Register (SPDR) contains information about drugs prescribed and dispensed in Sweden. Registrations include Anatomic Therapeutic Chemical classification system (ATC) codes, drug doses, package size, dates and the prescriber's profession and practice. Participation is mandatory for all pharmacies in Sweden.

Health-related Quality of life

Measuring Health-related Quality of Life

Quality of life (QoL) is a multidimensional concept that describes the subjective perception and evaluation of positive and negative aspects of life[81]. Quality of life can therefore by definition only be assessed by the individual patient and is influenced by expectations[82]. The term Health-related Quality of life (HRQoL) is used to evaluate if a specific treatment or illness affects a patient's well-being. Except for tumour response and survival, HRQoL is an important parameter to evaluate in the assessment of disease and treatment effects. Most scales used in clinical practice aggregate into four dimensions: physical, functional, emotional and social[83].

Patients might give different answers to HRQoL over time because of altered health status, but also because of adaptation and changed perception of the disease after a period of time. The latter is referred to as response shift[84].

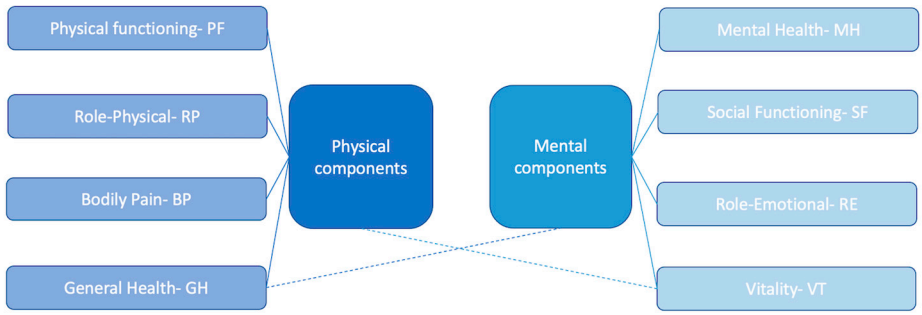

Figure 4
SF-36 scales [85]

The 36-Item Short Form Health Survey (SF-36) is a self-administrated, validated, generic instrument designed to assess general health. SF-36 is not specific to disease or treatment or age[86-88]. SF-36 consists of 36 questions grouped in eight domains: physical functioning (PF), bodily pain (BP), role limitations due to physical health problems (role-physical, RP), role limitations due to emotional health problems (role-emotional, RE), mental health (MH), social functioning (SF), energy or vitality (VT) and general health (GH). These profiles are combined into two summary measures: physical component summary (PCS) and mental component summary (MCS)[85]. The results are transformed to scores 0 to 100, with higher values representing better QoL.

Health-related Quality of Life in adrenal surgery

The increase in detection of adrenal incidentalomas combined with preoperative diagnostic challenges has consequently led to a considerable number of patients that undergo diagnostic adrenalectomy. Thus, survival and decreased risk for morbidity are not sufficient as outcome measures after adrenalectomy. HRQoL is an important factor.

HRQoL has only been studied scarcely in patients with adrenal disease[89]. Previous studies have indicated a reduced QoL irrespective of hormonal function[89]. Patients

with non-functioning incidentalomas were reported to have impaired QoL compared to healthy controls[90]. Few studies have focused on HRQoL before and after adrenal surgery. One report demonstrated improvement in QoL after adrenalectomy in physical but not mental domains[91]. General improvements in QoL have been demonstrated in patients with primary aldosteronism[92, 93].

Aims

In this thesis, clinical aspects of adrenalectomy were studied to investigate the effects of adrenalectomy for different adrenal conditions.

Specific aims:

I. To evaluate risk factors for complications, conversion from endoscopic to open adrenalectomy and prolonged hospital stay after adrenalectomy in a national cohort of patients.

II. To evaluate HRQoL in patients with functioning, non-functioning and malignant adrenal tumours before and after adrenalectomy.

III. To evaluate the impact of adrenalectomy on morbidity in patients with CS, ACS and non-functioning adrenocortical adenoma.

IV. To investigate clinical and surgical outcome in patients undergoing adrenalectomy with a final histological diagnosis of phaeochromocytoma. A special focus was to analyse outcome for phaeochromocytomas detected by clinical symptoms or as incidentalomas, and in patients with or without preoperative treatment with alpha-blockers

Methods

An overview of the methods used in papers I-IV is presented in Table 2.

Table 2
Overview of the papers

Paper	I	II	III	IV
Design	Retrospective observational study	Prospective observational study	Retrospective cohort-study	Retrospective observational study
Participants	Patients undergoing adrenalectomy 2009-2014 registered in SQRTPA (n=659)	Patients undergoing adrenalectomy at Lund University Hospital, Nov 2013-March 2017 (n=50)	Patients with CS, ACS or non-functioning adrenocortical adenoma undergoing adrenalectomy 2009-2017 and registered in SQRTPA (n=271) 1:3 age- and sex matched controls	Patients with phaeochromocytoma undergoing adrenalectomy Jan 2015-March 2020 registered in Eurocrine (n=551)
Outcomes	Risk factors associated with conversion rate, complication rate and length of hospital stay	HRQoL before and after adrenalectomy HRQoL depending on indication for surgery, hormonal hypersecretion and histopathology	Impact of adrenalectomy on morbidity in patients with CS, ACS and non-functioning adrenocortical adenoma	Differences in clinical- and surgical outcome in patients with subclinical- and symptomatic phaeochromocytoma Impact of preoperative treatment with alpha-adrenergic blockade on outcome
Data collection methods	Data variables collected from SQRTPA	Data variables collected from SQRTPA including SF-36	Data variables collected from SQRTPA, The Swedish National Patient register and The Swedish Prescribed Drug register	Data variables collected from Eurocrine
Data analysis	Binary logistic regression analysis Multiple linear regression analysis	Paired samples t test Wilcoxon´s Rank-Sum test Independent samples *t* test Mann-Whitney U test Minimally important difference for clinical significance	Chi-squared test Student´s *t* test Wilcoxon´s Rank-Sum test Incidence density rate	Chi-squared test Independent samples *t* test Mann-Whitney U test

Data collected were analysed using IBM SPSS Statistics 22 for Windows (IBM Corporation, Armonk, NY, USA), IBM SPSS Statistics for Mac, Version 26.0, Armonk, NY: IBM Corp, STATA/SE 13.1 for Mac (StataCorpLp, College Station, USA) and STATA v16.1 (Stata Corp. 2019, Stata Statistical Software: Release 16, College Station, TX: StataCorp LLC).

Definitions

Subclinical adrenal disease is an adrenal disease without symptoms or clinical signs, incidentally detected.

Surgical technique is registered in SQRTPA and Eurocrine® as laparotomy, open retroperitoneal-, transabdominal endoscopic-, transabdominal robotic-assisted-, posterior endoscopic-, posterior robotic-assisted- or thoracoabdominal approach. In paper I, III and IV the techniques were grouped depending on analysis:

Open adrenalectomy (laparotomy, open retroperitoneal- and thoracoabdominal approach)

Endoscopic adrenalectomy (transabdominal endoscopic-, transabdominal robotic-assisted-, posterior endoscopic- and posterior robotic-assisted approach)

Laparoscopic adrenalectomy (transabdominal endoscopic- and posterior endoscopic approach)

Robotic-assisted adrenalectomy (transabdominal robotic-assisted- and posterior robotic-assisted approach)

In paper I-IV complications specific to adrenal surgery were defined according to predefined data fields (bleeding with transfusion, laceration of viscus, pneumothorax and local infection) and as free-text with ICD-codes registered in SQRTPA and Eurocrine®. In paper IV postoperative complications graded according to the Clavien-Dindo classification system were added (available and mandatory as of 2015)[94].

Postoperative length of hospital stay (LOS) is the total number of days in hospital after adrenalectomy.

There was variability in time to follow-up depending on local variations in the management of the patients. The first follow-up was performed approximately four-six weeks after adrenalectomy and late follow-up six-twelve months after surgery.

A p value <0.05 was considered significant.

Paper I

Paper I was a retrospective observational study based on register data from the national quality register for endocrine surgery, SQRTPA, and analysed risk factors for complications, conversion to open surgery and LOS in patients undergoing adrenalectomy.

Patients

Patients undergoing adrenalectomy 2009-2014 registered in SQRTPA were included in the study.

Variables

Variables extracted from the quality register were:

Preoperatively: Type of hospital (university hospital or county hospital), sex, age, body mass index (BMI), hypertension, tumour side, radiological tumour size

Perioperatively: Indication for surgery, surgical technique, conversion from endoscopic to open surgery, surgical complications, LOS, 30-day mortality and histopathology

Statistics

Binary logistic regression analysis was performed to assess the association between outcome variables (complication or not, conversion or not, LOS in two groups (1-3 days or 4-39 days), endoscopic- or open adrenalectomy, laparoscopic- or robotic-assisted adrenalectomy) and predictors (variables mentioned above). Results were shown with odds ratios (OR) with 95% confidence intervals (CI).

Forward multiple linear regression analysis was performed to assess whether any variable influenced each outcome variable independently.

Paper II

Paper II was a prospective observational study evaluating HRQoL in patients with different adrenal conditions undergoing adrenalectomy as part.

Patients

Patients undergoing adrenalectomy November 2013-March 2017 at the Department of Surgery, Skåne University Hospital, Lund were offered participation in the study. Patients were invited at their first visit to the outpatient clinic when adrenalectomy was

planned. The study was performed as part of an agreed pilot module of patient-reported outcome measures (PROMS) for the SQRTPA. The patients were included by written consent and by completing and returning two SF-36 questionnaires. Questionnaires were administrated by mail approximately two weeks before and one year after adrenalectomy. One reminder was sent by mail to non-responders.

Responders and non-responders were compared regarding patient and tumour characteristics.

The Swedish manual and interpretation guide on SF-36 provided data from the general Swedish population collected 1991-1992, which was used as reference[95].

Data collection

SF-36 provided data on HRQoL. Patient and clinical data such as age, sex, indication for surgery, tumour characteristics and operative outcome were extracted from SQRTPA.

Statistics

The results from SF-36 were transformed to a score between 1-100 according to the manual, with higher values representing better QoL. Missing values were handled according to the SF-36 manual and substituted as a person-specific estimate when at least 50 per cent in a specific domain were answered[95]. If less than 50 per cent were answered, the score for that scale was set to missing. Clinical relevance was determined by using minimally important difference (MID) as a complement to statistical significance. A difference of 5-10 points on a 0-100-point scale was considered small, 10-20 points moderate and >20 large, according to Osoba et al[96].

Analyses were based on indication for surgery and histopathology and patients were grouped as benign non-functional tumours, benign functional tumours or malignant tumours. Pre- and postoperative SF-36 scores were assessed using paired samples *t* test or Wilcoxon´s Rank-Sum test for data with normal or skewed distribution, where appropriate. Differences between different patient groups and the control group were tested using independent samples *t* test or Mann-Whitney U test for data with normal or skewed distribution, where appropriate.

Paper III

Paper III was a retrospective cohort study which investigated the impact of adrenalectomy on morbidity in patients with CS, ACS and non-functioning adrenocortical adenoma as assessed by national and quality registers.

Patients

Patients undergoing adrenalectomy due to CS, ACS or non-functioning adrenocortical adenoma, registered in SQRTPA 2009-2017 were included in the study. The diagnosis was based on preoperative laboratory findings and histopathology.

Data collection

Demographic data, perioperative data and tumour characteristics were extracted from SQRTPA.

To evaluate morbidity pre- and postoperatively the Swedish National Patient Register and the Swedish Prescribed Drug Register provided data on inpatient diagnoses and dispensed drug prescriptions. Drugs used for the treatment of disorders related to cortisol hypersecretion were identified through the ATC-codes. Defined daily dose (DDD) was used to calculate drug consumption per patient and year. The International Statistical Classification of Diseases and Related Health Problems - Tenth Revision – Sweden (ICD-10-SE) was used to collect inpatient diagnoses related to known morbidity in patients with CS. A control group matched by age and sex, with three controls per patient, was produced by Statistics Sweden[97].

Statistics

Differences between the tumour groups and with the control group were evaluated. Data on drug use was analysed by pairwise comparison one year before and one year after adrenalectomy and by comparing changes in group means one year before adrenalectomy, and annually after adrenalectomy. Inpatient diagnoses, gathered in disease groups, were analysed as calculated pre- and postoperative incidence density rates of disease. Incidence density rates of disease were defined as the sum of diagnoses in each disease group relative to the amount of person-time at risk (i.e., from start of follow up to surgery and from surgery to end of follow up). The confidence intervals were calculated under the assumption of a Poisson distribution.

Statistical hypothesis tests were performed using Chi-squared test for categorical variables and Student´s *t* test or Wilcoxon´s Rank-Sum test for continuous variables.

Paper IV

Paper IV was a retrospective observational study based on register data extracted from the European quality register for endocrine surgical procedures, Eurocrine®. The study evaluated differences in clinical and surgical outcome in patients with subclinical- and symptomatic phaeochromocytoma and the clinical significance of preoperative treatment with alpha-adrenergic blockade.

Patients

Patients with histological diagnosis of phaeochromocytoma, undergoing adrenalectomy and registered in Eurocrine® from January 1st 2015 to March 31st 2020 were included in the study. Patients with reoperations were excluded.

Variables

Variables extracted from the quality register were:

Preoperatively: Sex, age, BMI, hypertension, diabetes, hereditary disease, tumour detection, radiological evaluation and hormonal evaluation

Perioperatively: Indication for surgery, surgical technique, preoperative alpha-blockade, conversion from endoscopic to open surgery, complications, LOS and histopathology

Statistics

Comparisons between groups were based on indication for surgery (catecholamine excess or not) and tumour detection (symptomatic- or incidental disease) and treatment with alpha-adrenergic blockade or not. Differences between patient groups were evaluated using Chi-squared test for categorical data. Continuous data was compared using independent samples *t* test or Mann-Whitney U test for data with normal and skewed distribution where appropriate.

Ethics

Paper I and II

These studies were part of a routine quality control program within the national quality register- SQRTPA. Quality control and analysis of a feasibility pilot of PROMs for the register were performed according to Swedish legislation for health care providers.

Paper III

The study was approved by the Regional Ethics Committee at Lund University, Sweden (No. 2017/800).

Paper IV

The study was approved by the Regional Ethics Committee at Lund University, Sweden (No. 2018/1054).

Results

Paper I

A total of 659 patients underwent adrenalectomy during the study period distributed among five university hospitals, 639 (97 per cent) patients and five county hospitals, 20 (three per cent) patients. The majority of the patients were women, 372 (56 per cent) patients, the median age was 59 years.

The most common indication for surgery was hormonal excess, 399 (61 per cent) patients. Minimal invasive surgery was performed in 513 (78 per cent) patients, equally distributed between laparoscopic- and robotic-assisted adrenalectomy. Conversion rate was 7.2 per cent (37 patients). Overall complications were 6.5 per cent (43 patients) and LOS was 3 days. There was no 30-day mortality.

Complication after adrenalectomy

The number of complications was low. In the binary regression analysis large tumour, OR 1.01 (CI 1.01-1.02), open adrenalectomy, OR 2.61 (CI 1.29-5.28) and conversion from endoscopic- to open adrenalectomy, OR 2.89 (CI 1.14-7.34) were associated with an increased number of complications. In the subsequent multivariable analysis, only conversion to open surgery was predictive for an increased risk of complications, OR 3.61 (CI 1.07-12.12).

Conversion to open surgery

Conversion from endoscopic- to open surgery was uncommon. In the binary regression analysis, the risk for conversion was associated with robotic-assisted surgery, OR 5.14 (CI 1.46-18.11), but in the multivariable analysis large tumour, OR 1.03 (CI 1.0-1.06) and malignant tumours, OR 8.33 (CI 2.12-32.07) were the only variables predictive of conversion.

Length of Hospital stay

The median LOS was three days but with some patients hospitalized for a long time, range 1-30 days. Several factors were associated with a longer hospital stay in the binary

analysis: age, larger tumours, open surgery, malignant tumours and conversion to open surgery. In the multivariable regression analysis conversion to open surgery, OR 42.05 (CI 5.02-352.40), open adrenalectomy, OR 115.18 (CI 32.94-402.67), excess of catecholamines, OR 2.32 (1.18-4.59), bilateral tumour, OR 3.13 (CI 1.08-9.06) and tumours in the left adrenal gland, OR 1.98 (CI 1.14-3.43) were independent predictive factors for longer hospital stay.

Surgical technique

As suspected large tumour, OR 1.06 (CI 1.04-1.07) and malignant histopathology, OR 11.13 (CI 4.82-25.70) were predictive factors for open surgery when compared with endoscopic surgery.

When comparing endoscopic techniques, larger tumours were associated with robotic-assisted adrenalectomy, OR 1.02 (CI 1.01-1.03).

Paper II

Of 161 eligible patients, 50 (31 per cent) patients returned two complete SF-36 questionnaires and were included in the study. Half of the patients, 26 (52 per cent) were women and the median age was 64 years. There were no statistical differences between the patients included in the cohort and non-responders regarding patient and tumour characteristics (data not shown).

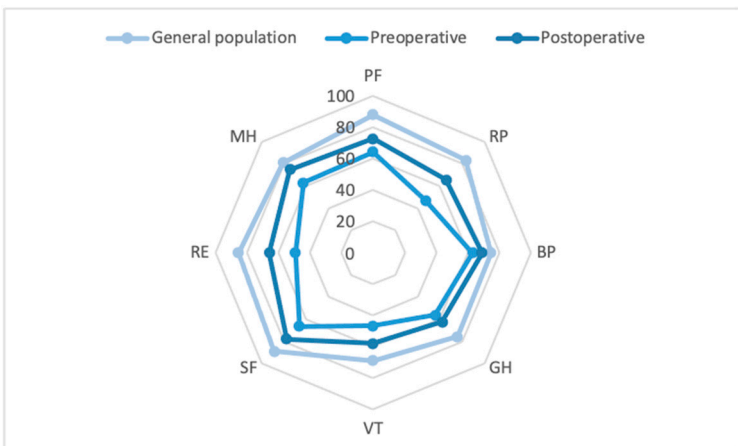

Figure 5
SF-36 for all patients before and after adrenalectomy and the general Swedish population (100 is the best outcome).

All patients

Compared with the general Swedish population the patients reported lower HRQoL both pre- and postoperatively except for BP (bodily pain) after adrenalectomy. These differences were more pronounced preoperatively and the clinical significance was interpreted as moderate or large. Patients reported a higher HRQoL after adrenalectomy compared to before surgery in all dimensions except for BP, both statistically and clinically (Fig 5).

Different disease groups

Patients with benign functional tumours had lower SF-36 scores before and after adrenalectomy compared with the general Swedish population and preoperatively when compared with patients with benign non-functional tumours. Patients with benign functional tumours reported improved HRQoL after adrenalectomy. All comparisons were clinically significant with a difference larger than 20 points seen on all SF-36 scores (Table 3). These improvements were not shown for any other disease group (benign non-functional tumours or malignant tumours). Interestingly, patients with benign non-functional tumours reported lower SF-36 scores preoperatively compared with the general Swedish population, but improvements were absent postoperatively (Fig 6). No major differences could be detected between patients with malignant and benign non-functional tumours.

Table 3
SF-36 scores in patients with benign functional tumours before and at one year after adrenalectomy. Median (range) is shown.

	Preoperative (n=29)	Postoperative (n=29)	*p* value
Physical functioning	60 (10-100)	80 (10-100)	0.011
Role-Physical	0 (0-100)	100 (0-100)	0.003
Bodily pain	41 (10-100)	84 (21-100)	0.005
General health	47 (0-87)	67 (0-100)	0.036
Vitality	35 (0-100)	70 (5-100)	0.001
Social functioning	62.5 (0-100)	100 (0-100)	0.024
Role-Emotional	33.3 (0-100)	100 (0-100)	0.031
Mental health	52 (0-100)	84 (20-100)	0.001
Physical Component Summary	33.1 (17.1-62.9)	47.6 (19.8-57.3)	0.005
Mental Component Summary	33.8 (11.8-62.0)	52.7 (16.4-59.8)	0.004

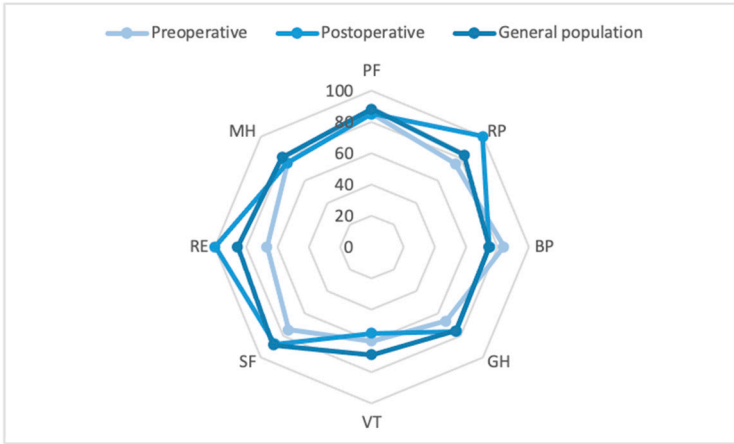

Figure 6
SF-36 for patients with non-functional tumours before and after adrenalectomy and the general Swedish population (100 is the best outcome).

Paper III

Patients

A total of 271 patients with CS, ACS and non-functioning adrenocortical adenoma underwent adrenalectomy during the study period. Statistic Sweden added 813 matched controls.

Some expected differences were detected among the patient groups. Patients with CS were younger, had a larger proportion of women and tumours were more often detected by symptoms. Patients with CS were also diagnosed more frequently with bilateral tumours and adrenal hyperplasia compared with the other tumour groups. As expected, hypertension was common but interestingly with a frequency of approximately 50 per cent *regardless* of the tumour group.

Morbidity evaluated with medication

Medication for hypertension was more frequent in patients with CS, ACS and non-functioning adrenocortical adenoma compared with the control group (Table 4). Interestingly medication for hypertension increased the first year after adrenalectomy, followed by a distinct decrease over time (Fig 7a) (Table 5).

For the medications studied, there were no major differences among patients with CS and ACS. Patients with CS and ACS medicated with drugs for hyperlipidaemia, osteoporosis and depression more often compared with the control group before

adrenalectomy. In contrast to the other patient groups, medication for diabetes and hyperlipidaemia remained constant during follow-up for patients with ACS.

Table 4
Defined daily dose (DDD) per patient per year, one year before adrenalectomy in the patient groups and controls. Grouped according to ATC-codes. Mean and standard deviation (SD) is shown.

	CS n=127	ACS n=45	NFAA n=99	Control group n=813	CS vs. ACS *p* value	CS vs. NFAA *p* value	CS vs. Control group *p* value	ACS vs. NFAA *p* value	ACS vs. Control group *p* value	NFAA vs. Control group *p* value
Hypertension	572.3 (928.0)	465.5 (719.6)	345.1 (495.6)	236.1 (477.3)	0.484	0.029	<0.001	0.246	0.002	0.033
Diabetes	73.5 (197.8)	109.1 (310.2)	91.2 (320.1)	39.6 (201.7)	0.379	0.611	0.077	0.755	0.030	0.026
Hyperlipidaemia	152.3 (378.6)	133.0 (257.0)	114.1 (269.3)	64.8 (212.4)	0.752	0.397	<0.001	0.693	0.038	0.035
Osteoporosis	35.5 (120.2)	39.2 (102.3)	6.8 (39.2)	7.6 (56.6)	0.854	0.023	<0.001	0.007	<0.001	0.893
Antibiotics	11.1 (22.2)	11.0 (19.6)	7.9 (16.4)	7.3 (31.4)	0.986	0.225	0.186	0.314	0.427	0.854
Depressive disease	136.4 (299.4)	101.9 (278.6)	67.2 (169.7)	38.4 (156.9)	0.501	0.041	<0.001	0.358	0.012	0.088

CS Cushing´s syndrome, *ACS* Autonomous cortisol secretion, *NFAA* Non-functioning adrenocortical adenoma

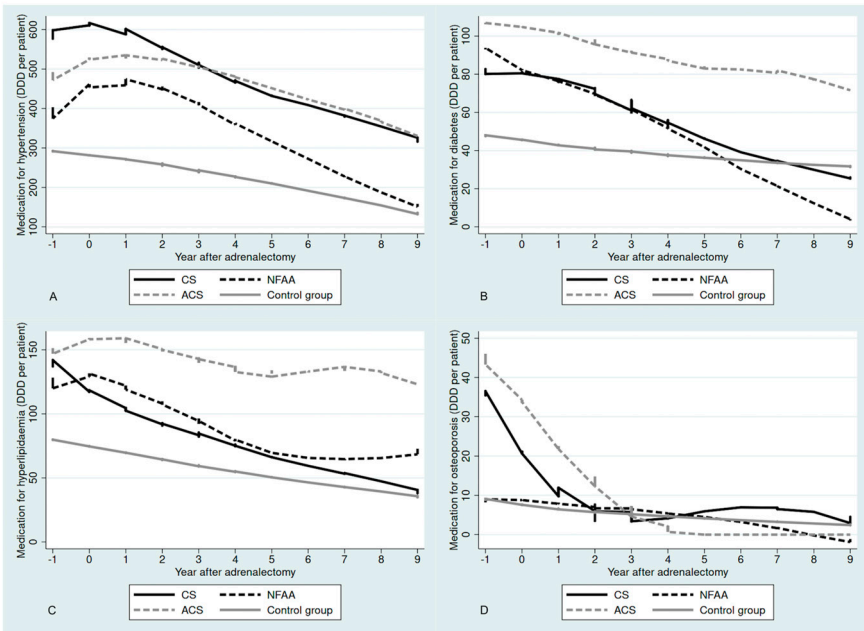

Figure 7a-d
Medication for hypertension, diabetes, hyperlipidaemia and osteoporosis one year before- and annually after adrenalectomy. *CS* Cushing´s syndrome, *ACS* Autonomous cortisol secretion, *NFAA* Non-functioning adrenocortical adenoma. (Reprinted with permission)

Table 5
Differences in drug consumption one year before and one year after adrenalectomy for patients and controls with medication grouped according to anatomical therapeutic chemical (ATC) codes. Mean difference (DDDpost-DDDpre) and standard deviation in defined daily dose (DDD) per patient per year is shown.

	CS n=127		**ACS n=45**		**NFAA n=99**		**Control group n=813**	
	DDD, mean difference (SD)	*p* value	DDD, mean difference (SD)	*p* value	DDD, mean difference (SD)	*p* value	DDD, mean difference (SD)	*p* value
Hypertension	198.4 (728.1)	0.003	96.4 (598.4)	0.286	184.2 (510.0)	<0.001	-11.3 (364.2)	0.378
Diabetes	22.8 (184.7)	0.166	-10.6 (164.7)	0.668	-9.6 (193.9)	0.624	-3.7 (90.4)	0.249
Hyperlipidaemia	-59.4 (306.6)	0.013	81.6 (389.2)	0.167	29.2 (268.3)	0.281	-3.7 (138.5)	0.450
Osteoporosis	-14.3 (102.7)	0.119	7.5 (51.5)	0.336	5.7 (31.0)	0.072	-2.1 (47.1)	0.198
Antibiotics	3.5 (47.9)	0.412	-2.5 (22.5)	0.464	2.5 (19.8)	0.205	-0.2 (20.6)	0.776
Depressive disease	-30.3 (226.7)	0.134	-47.6 (153.2)	0.043	4.1 (171.5)	0.814	-1.0 (9.2)	0.784

CS Cushing´s syndrome, *ACS* Autonomous cortisol secretion, *NFAA* Non-functioning adrenocortical adenoma

Morbidity evaluated with inpatient diagnosis

No major differences in morbidity were detected among the patient groups or referents as evaluated by ICD-10 codes. Incidence density rates for ischemic heart disease were higher in all groups after adrenalectomy (Fig 8).

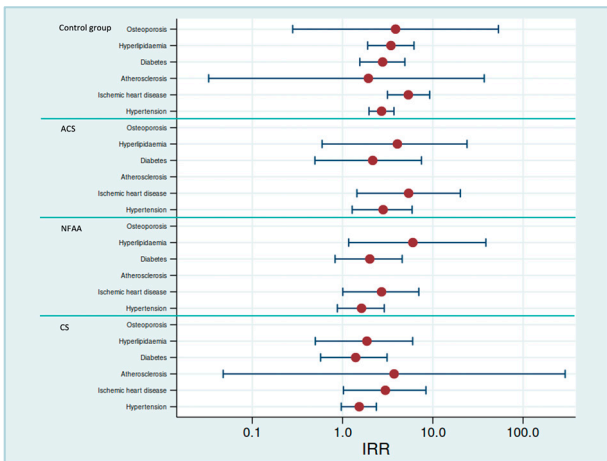

Figure 8
Incidence rate ratio (IRR) for different disease groups in the tumour groups and controls. *CS* Cushing´s syndrome, *ACS* Autonomous cortisol secretion, *NFAA* Non-functioning adrenocortical adenoma. (Reprinted with permission)

Paper IV

Some 551 patients were included in the study. Patients were distributed over 48 surgical departments in 11 countries. The mean age was 53 years, and 319 (58 per cent) patients were women.

Patients

Nearly half of the tumours were detected as incidentalomas, 239 (43 per cent) patients. In 486 (88 per cent) patients, the indication for surgery was catecholamine excess and preoperative alpha-blockade was used in 366 (84 per cent) patients. Complications according to Clavien-Dindo was four per cent (22 patients) and only 5 per cent (22 patients) of endoscopic surgical procedures were converted to open surgery.

No major differences in surgical outcome were detected related to alpha-blockade or not: complications (according to Clavien-Dindo), 12/366 patients (3 per cent) vs. 0, *p* 0.625, and conversion, 13/327 patients (4 per cent) vs. 3/56 patients (5 per cent), *p* 0.633.

Table 6
Characteristics and outcome in patients with phaeochromocytoma preoperatively diagnosed with catecholamine excess or with other indications for surgery.

	Preoperatively diagnosed phaeochromocytoma (n=486)	**Other indications for surgery (n=65)**	***p* value**
Age (years), mean (s.d.)	52.7 (15.9)	56.7 (16.0)	0.058
Sex (female), n (%)	280 (57.6)	39 (60.0)	0.714
Hypertension, n (%)	238 (49.0)	27 (41.5)	0.260
Incidentaloma, n (%)	182 (37.4)	57 (87.7)	<0.001
CT, n (%)	215 (44.2)	43 (66.2)	0.001
Other indications for surgery			
-Suspicious for malignancy on radiological examination, n (%)	139/475 (29.3)	39/64 (60.9)	<0.001
-Size only, n (%)	10/441 (2.3)	6/59 (10.2)	0.001
-Suspicious for metastasis, n (%)	4 (0.8)	2 (3.1)	0.100
Preoperative alpha blockade, n (%)	350/385 (90.9)	16/52 (30.8)	<0.001
Surgical technique, n (%)	(n=479)	(n=63)	0.623
-Open	51 (10.6)	8 (12.7)	
-Endoscopic	428 (89.4)	55 (87.3)	
Conversion, n (%)	18/428 (4.2)	4/55 (7.3)	0.304
Complication[a], n (%)	19 (3.9)	3 (4.6)	0.785
Histopathology, n (%)			
-Malignant phaeochromocytoma	13 (2.7)	3 (4.6)	0.382

This table is redesigned and adjusted, not all variables as in the original paper are listed above.

Analysis based on the indication for surgery

Symptomatic disease was more frequent in patients with catecholamine excess as the indication for surgery than patients registered with other indications for surgery. Preoperatively diagnosed phaeochromocytomas were more frequently treated with preoperative alpha-blockade (Table 6).

Analysis based on tumour detection

Patients with incidentally detected phaeochromocytomas had less frequently hypertension compared with patients with symptomatic disease, 91 (38 per cent) patients vs. 174 (56 per cent) patients. Alpha-blockade was more often used in patients with symptomatic phaeochromocytomas than in patients diagnosed as incidentalomas. There were no major differences in surgical technique or surgical outcome among the two subgroups of patients (Table 7).

Table 7
Characteristics and outcome in patients with phaeochromocytoma diagnosed as adrenal incidentalomas or with adrenal related symptoms.

	Incidentaloma (n=239)	Adrenal related symptoms (n=312)	*p* value
Age (years), mean (s.d.)	56.8 (15.1)	50.4 (16.1)	<0.001
Sex (female), n (%)	147 (61.5)	172 (55.1)	0.133
Hypertension, n (%)	91 (38.1)	174 (55.8)	<0.001
Indication, n (%)			
-Catecholamine excess	182 (76.2)	304 (97.4)	<0.001
CT, n (%)	154 (64.4)	104 (33.3)	<0.001
Preoperative alpha blockade, n (%)	150/198 (75.8)	216/239 (90.4)	<0.001
Surgical technique, n (%)	(n=238)	(n=304)	0.173
-Open	21 (8.8)	38 (12.5)	
-Endoscopic	217 (91.2)	266 (87.5)	
Conversion, n (%)	8/216 (3.7)	14/267 (5.2)	0.420
Complication free-text, n (%)	6 (2.5)	16 (5.1)	0.120
Complication Clavien-Dindo, n (%)			0.810
-Grade I	20 (8.4)	28 (9.0)	
-Grade II	4 (1.7)	9 (2.9)	
-Grade III	2 (0.8)	2 (0.6)	
-Grade IV	1 (0.4)	3 (1.0)	
LOS (days, median (i.q.r.))	(n=238) 3 (2-5)	(n=310) 3 (2-5.25)	0.400
Histopathology, n (%)			
-Malignant phaeochromocytoma	8 (3.3)	8 (2.6)	0.587

This table is redesigned and adjusted, not all variables as in the original paper are listed above.

Discussion

Adrenal incidentalomas (AI) are common within the population. The rate of AI in imaging performed for non-adrenal reasons has increased to approximately one to four per cent[1, 2]. The majority of the tumours are benign adrenocortical adenomas, but some are malignant or associated with hormonal hypersecretion.

There has been a trend towards more frequent adrenal surgery as a consequence of the increased detection rate of AI and the use of minimally invasive surgical techniques[98]. However, the increase in adrenal surgery has not been associated with an increase in detection of ACC and thus some operations are probably questionable[99]. Multidisciplinary diagnostic and care teams are recommended to treat the increasing number of patients with adrenal tumours. Several international and national guidelines for the management of AI are available[7].

This thesis covers a spectrum of important aspects to consider in clinical practice for patients with adrenal disease.

The optimal management of patients with ACS and non-functioning adrenocortical tumours is unclear. Despite increased risk for cardiovascular morbidity, it is not clarified whether these patients benefit from adrenalectomy. Consequently, the potential value of adrenalectomy should be balanced against the risks of surgery and HRQoL. Perioperative management of patients with phaeochromocytomas are controversial. Routine preoperative alpha-adrenergic blockade has recently been challenged due to modern anaesthetic methods and minimally invasive surgery.

This thesis shows that adrenalectomy is a safe procedure with a low rate of intraoperative complications regardless of underlying disease. Perioperative alpha-blockade did not affect the surgical outcome in patients with phaeochromocytoma. The thesis also shows that hypertension is common in benign cortical tumours regardless of cortisol hypersecretion or not, and medication for hypertension decreased for both patient groups postoperatively. Interestingly, patients with benign non-functioning tumours did not report improved HRQoL after adrenalectomy.

Adrenalectomy and perioperative outcome

Adrenalectomy has a low mortality rate. In **paper I** the 30-day mortality was nil which is comparable to other studies[65].

Factors that may influence risk for complication are patient- or surgery related. Some examples of patient-related factors are age, sex, comorbidities, BMI, tumour type and tumour size. Important surgery-related factors are the experience of the individual surgeon, hospital volumes of adrenal surgery and surgical technique.

Transabdominal laparoscopic adrenalectomy is the standard treatment for adrenal tumours in many centres[67]. The benefits compared to open surgery include a shorter length of stay postoperatively and fewer surgical and nonsurgical complications[66, 100]. The endoscopic techniques have evolved and now include posterior retroperitoneal- and robotic-assisted techniques with similar favourable results. Thus, the choice of surgical technique is determined by the surgeon on the basis of surgical experience and available equipment.

However, in spite of an increasing number of operations, adrenalectomy is an uncommon procedure, in Sweden, approximately 200 adrenalectomies in 2020. It may prove difficult for the individual surgeon to overcome the learning curve for the procedure, which is estimated to approximately 30 laparoscopic procedures[101, 102], especially for larger tumours[75]. It may therefore be wise to adhere to one specific endoscopic technique. Available recommendations suggest at least six adrenalectomies per year in a single centre to minimize complications and adhere to oncological principles[103, 104]. However, surgical sub-speciality, e.g., urology, general surgery or endocrine surgery has no significant impact on perioperative outcome[105, 106]. The impact of volume-outcome was not investigated in **paper I** since SQRTPA does not include individual volume data.

A wide range of perioperative complications related to adrenal surgery have been described. The most frequent intraoperative complications are bleeding including injury to the adrenal vein, vena cava injury, laceration of the spleen or diaphragm. The most common complications within 30 days postoperatively are retroperitoneal hematoma, incisional hernia, pancreatic fistula, hyponatraemia and intestinal injuries[107].

In **paper I,** bleeding with transfusion was the most frequent complication, followed by re-operation and surgical site infection. The reported complication rate, 6.5 per cent, is comparable with complications reported by others[75, 108, 109]. As reported in **paper I**, the only independent predictive factor for complication was conversion from

endoscopic to open surgery. The risk for conversion was related to tumour malignancy and tumour size. These results are important to consider when choosing surgical technique for the individual patient: open surgery may thus be preferred for some patients.

Surgical management of large adrenal tumours is a matter of debate. According to the literature laparoscopic adrenalectomy is recommended in tumours up to six cm, including suspected malignant tumours if there is no local tumour invasion on imaging and the surgeon has sufficient operative experience[7, 51]. However, laparoscopic surgery in patients with tumour size up to ten cm has been suggested[76]. Recent reports indicate improved surgical outcome with robotic-assisted adrenalectomy compared with laparoscopic adrenalectomy in larger adrenal masses[110]. Further, posterior retroperitoneal technique is mainly preferred for smaller tumours[72].

In **paper I** almost half of the operations were robotic assisted. The technique was used in older patients and patients with larger tumours. Bergamini et al, showed that BMI is a risk factor for complications[111]. Some advantages for robotic surgery in obese patients have been shown[112]. However, BMI was not predictive for the use of robotic-assisted surgery in this study.

When evaluating surgical results several aspects should be considered such as the effectiveness of the treatment, complications, prognosis, long term morbidity and HRQoL. Costs and available surgical techniques are also important. Equipment for laparoscopic surgery is available in most surgical departments, which makes the technique fairly cheap. Robotic-assisted surgery offers better precision, tremor filtration and enhanced ergonomics for the surgeon compared to conventional laparoscopy but comes with higher costs[113, 114]. Three-dimensional (3D) laparoscopic techniques as well as robotic-assisted techniques have shorter learning curves than 2D techniques, which may be advantageous in centres with lower volumes of surgery[114, 115].

Health-related Quality of Life and adrenalectomy

Survival, surgical result and cure are outcome measures easy to evaluate and to be understood by the clinician. Complications or side effects are not always taken into account. Overall, data on the impact of adrenalectomy on HRQoL in patients with adrenal tumours are scant.

In **paper II** HRQoL was evaluated in patients with a variety of functional and non-functional adrenal tumours and benign or malignant tumours. In the patient cohort,

HRQoL increased after adrenalectomy in the physical and mental domains but remained lower compared with a large sample of the general Swedish population.

Patients with functional tumours had the greatest improvement after adrenalectomy. In agreement with **paper II**, some previous studies describe decreased HRQoL in patients with Cushing´s syndrome and primary aldosteronism with improvements after adrenalectomy[92, 93, 116]. Patients with mild ACS has been shown to improve HRQoL after adrenalectomy as evaluated with SF-36[117].

Interestingly, patients with benign non-functional tumours reported lower HRQoL compared with the general Swedish population preoperatively, but no improvement was detected after adrenalectomy. In patients with benign, small and hormonally inactive tumours logically HRQoL should not differ from the normal population. The reason may be that results are skewed by detection bias, i.e., patients with AI are investigated due to underlying symptoms or morbidity. However, it has also been suggested that these patients may harbour minor abnormalities in hormonal secretion not detectable with conventional biochemical methods. These hormonal abnormalities have been suggested to be associated with impaired health, but this hypothesis needs to be evaluated in larger studies[44, 50].

According to the findings in **paper II** patients with malignant disease reported HRQoL not different than patients with benign non-functional tumours. This may indicate that psychological factors such as anxiety and fear of malignant disease affect QoL. Interestingly it has been shown that HRQoL was decreased in patients with thyroid cancer many years after diagnosis in spite of an excellent prognosis[118].

Adrenalectomy and morbidity in mild hypercortisolism

The main purpose of **paper III** was to evaluate the impact of adrenalectomy on morbidity related to cortisol excess in a large series of patients with mild hypercortisolism. Treatment guidelines recommend an individual approach based on age, the level of cortisol secretion, comorbidities, general health and the patient´s preferences[7].

Autonomous cortisol secretion was described as pre-Cushing´s syndrome in a patient report by Charbonnel et al in 1981[119]. The authors reported a pathologic dexamethasone suppression test with partially suppressed ACTH despite normal plasma and urinary cortisol levels in a patient with an adrenal tumour and no clinical signs of adrenal disease. Hormone levels were normalised eight months after excision of the adrenal adenoma. The term pre-clinical Cushing´s syndrome inherently

implicates a progression to manifest Cushing´s syndrome which however has been shown to be rare. The term pre-clinical Cushing´s syndrome has been replaced by subclinical Cushing´s syndrome, mild hypercortisolism, subclinical hypercortisolism and lately the currently recommended term, autonomous cortisol secretion, ACS[7, 120].

During the last two decades, several studies have demonstrated increased morbidity in patients with ACS, similar to that of CS, and curiously enough in patients with non-functioning adrenocortical adenomas.

ACS is a recently discovered disease and there is no international consensus regarding the biochemical definition of the disease. Guidelines and recommendations are based mainly on retrospective studies[14, 121, 122]. It has been debated if non-functioning adrenocortical adenomas and ACS are part of a biochemical spectrum and hence different stages of the same disease[49]. Non-functioning adrenocortical adenomas are usually diagnosed when cortisol levels after 1-mg dexamethasone suppression test are <50 nmol/L and this was the definition used in **paper III**. However, it has been suggested that the 1-mg dexamethasone suppression test may not be sensitive enough. Cut-off values 33-41 nmol/L has been suggested since an increased risk of insulin resistance, cardiovascular events and postoperative adrenal insufficiency has been shown at the threshold used in the present study[50, 123, 124]. Unfortunately, exact values for cortisol and ACTH are not available in SQRTPA, and hence this could not be evaluated in the present investigation.

In **paper III** there were no major differences in medication before adrenalectomy for patients with ACS compared with patients with non-functioning adrenocortical adenoma except for osteoporosis. A possible explanation for the increased morbidity in patients with non-functioning adrenocortical adenomas may be that this group of patients is more likely to undergo abdominal imaging for symptoms or other morbidities. However, a decrease in drug consumption for hypertension, diabetes and hyperlipidaemia was observed after adrenalectomy suggesting underlying adrenal disease. In contrast, in **paper II**, adrenalectomy had no impact on HRQoL in patients with benign non-functional adrenal tumours.

Patients with ACS exhibited similar morbidity- as evaluated with dispensed drug prescriptions- as patients with CS and this is in agreement with earlier reports. Medication for hypertension, hyperlipidaemia, diabetes, osteoporosis and depression was higher in patients with ACS compared with controls. However, improvements in drug consumption could not be detected postoperatively in the short term in patients with ACS. This highlights again the importance of randomized controlled trials to evaluate the impact of adrenalectomy on morbidity in these patients.

The prevalence of hypertension in European countries is 25-44 per cent[125, 126]. A prevalence of approximately 70 per cent of hypertension in patients with non-functioning adrenocortical adenomas has been described[127]. In this study, the rate of hypertension was approximately 50 per cent in all patient groups and they were treated more often for hypertension compared with their respective controls. Distinct reductions in medication for hypertension were detected annually after adrenalectomy for the patient groups but was stable for controls.

Analysis of data from the National Patient Register in Sweden showed no large differences in morbidity based on ICD-codes. However, since many patients are not treated in-hospital for a number of the studied diseases, such as diabetes, hypertension, depression and infection, and due to lack of out-patient data in primary care, it is difficult to draw firm conclusions based on this finding.

Clinical and surgical outcome in phaeochromocytoma

A large proportion of phaeochromocytomas are discovered as adrenal incidentalomas without clinical symptoms of catecholamine excess. Guidelines recommend clinical and hormonal evaluation of all adrenal incidentalomas, including catecholamine secretion[7]. Despite this, some patients are only diagnosed postoperatively on final histopathology.

Untreated phaeochromocytoma may cause hypertensive crises in stressful situations and adrenalectomy is the recommended curative treatment[38]. Preoperative alpha-adrenergic blockade is recommended to prevent hemodynamic instability. The main purpose of **paper IV** was to investigate differences in clinical presentation and surgical outcome in a large, international series of patients with subclinical and symptomatic phaeochromocytoma. The study especially focused on modes of detection, diagnosis and the use of preoperative alpha-adrenergic blockade.

Almost half of the phaeochromocytomas were detected incidentally. This is in agreement with other reports[58, 128]. In Eurocrine® the mode of detection is a mandatorily registered variable with adrenal incidentaloma or adrenal related symptoms as possible alternatives for registration. Furthermore, hypertension is the only specific symptom requested. Possibly, other symptoms more difficult to evaluate such as headache, sweating and palpitations may affect registration.

Hypertension is frequent in phaeochromocytomas and was registered in almost 50 per cent of the patients. This is a fairly low figure compared with 78-94 per cent of patients with hypertension reported previously[58, 128]. One reason for this could be variations

in the definition of hypertension among studies. In **paper IV** hypertension was based on preoperatively measured blood pressure or known antihypertensive medication. However, some patients may be normotensive but with paroxysmal hormonal secretion with hypertensive peaks. The frequency of this is not known.

Plasma or urinary catecholamines were registered as elevated in 90 per cent of the patients preoperatively. More than 60 per cent of these patients were detected by symptoms. For patients with other indications for surgery (suspected malignancy on radiological evaluation, suspected metastasis, size only) only 16 per cent were symptomatic.

The role of alpha-blockade has been debated as anaesthetic methods and minimally invasive surgery has evolved. Results from observational studies are not unequivocal[39, 40]. The disadvantages of alpha-blockade consist of an increased risk for preoperative hospitalization due to hypotension, intraoperative and postoperative hypotension episodes after adrenal vein ligation and tumour excision with the patient needing massive volume infusion[129].

Interestingly, despite generally agreed recommendations, only 90 per cent of patients with known phaeochromocytoma were treated with alpha-adrenergic blockade preoperatively. Among patients who were not diagnosed with phaeochromocytoma preoperatively only 30 per cent were preoperatively prepared with alpha-blockade. There was no obvious difference in complications, conversions or length of stay related to preoperative alpha-blockade or not.

It has been proposed that patients with phaeochromocytoma and hypertension present higher levels of catecholamines than patients without hypertension[128]. Patients with subclinical phaeochromocytoma presented with a lower rate of increased catecholamines in plasma and urine compared with patients with clinical disease.

Aspects of methodology

Register-based studies and retrospective studies

In this thesis national and quality registers were used for data collection. Data retrieved from well-validated medical registers with high coverage may hence reflect general clinical practice[130].

Randomized controlled trials (RCTs) are generally regarded as the highest level of scientific evidence among study designs. However, RCTs are of inherently experimental design to explore mainly one factor in a homogenous group of patients

and might therefore differ from clinical reality. There are inherent limitations in the generalisability of outcomes. When estimating causal effects it is of importance not to infer that the target population is equal to the study sample[131]. High-quality observational studies may be beneficial in this regard. For instance, in observational studies, changes over time may be investigated which may generate hypotheses for future RCTs. Large cohorts collected prospectively, e.g., cancer registries and birth registries, can be used to study different outcomes. A register-based study is optimal to study risk factors and prognostic factors but requires a thorough evaluation of confounders, underreporting, erroneous data and missing data.

A retrospective study design is well suited for evaluating unusual diseases and therapies which would otherwise require too long inclusion period and follow up. Some other advantages include low costs and quick results[132]. However, even in modern registries with pre-defined data fields, data in retrospective observational studies are collected for other purposes and may lack relevant information for the focus of the study.

In RCTs, sample size calculations are essential to determine the number of patients needed to establish statistical power. In observational studies, sample size calculations are more complex and should, generally speaking, be avoided. In analyses based on large registries the risk of type II errors, i.e., not finding an existing difference, is considered low. It is therefore important to consider whether the results are clinically significant, regardless of statistical significance. Non-significance in observational studies may indicate insufficient power or no difference.

Confounders

A *confounder* is a factor that erroneously implies an association that is causal[132]. Randomization and matching are methods to handle confounding, but confounders can also be analysed statistically. In **paper I,** multiple logistic regression models were used to control for confounders.

Paper I aimed to report the national experience of adrenalectomy in Sweden and determine risk factors for complications, conversion from endoscopic to open surgery and prolonged hospital stay. Information was extracted from SQRTPA with predefined data fields and lack of some important variables, for instance, operative experience for the individual surgeon and some comorbidities and non-surgical complications. Additionally, missing values must be considered. SQRTPA is regularly validated by external audit and results have generally speaking been good[77].

In **paper III** SQRTPA was cross-linked with national registers on inpatient diagnoses and drug prescriptions. Data from the national registers capture some data on

comorbidity which is lacking in the quality register. Further, morbidity was evaluated with inpatient diagnoses although some of the studied diseases often are managed in the outpatient setting and primary care, for instance, hypertension and diabetes. Data on drug prescriptions, therefore, complement inpatient diagnoses for assessment of morbidity.

Selection bias

To minimize selection bias in **paper II**, patients were included consecutively. Mainly due to structural obscurity in terms of administration of the first questionnaire in the inclusion process, only 37 per cent of patients undergoing adrenalectomy during the study period were included in the study. This is a low figure. To evaluate the impact of the low number of participants, preoperative characteristics of the patients in the study were compared with non-included patients, without detected differences between the two groups.

Missing data

Missing data reduces the representativeness of the study sample and the statistical power. Attention must be given to the reasons for missing data. Imputation or omission are methods to handle missing data in the analysis. Data collection should be user friendly to reduce the amount of missing data, e.g., register-data fields and questionnaires easy to access and register. In this thesis, missing data were not included in the analysis of register data. In the analysis of SF-36 missing data were imputed with an estimate calculated scale by scale as recommended by the SF-36 Health Survey Manual.

Assessment of complications

Paper I and **IV** evaluated complications related to adrenalectomy. Initially, SQRTPA included only predefined data fields with certain complications combined with a free-text field for ICD-codes. This may complicate comparisons with other studies. Currently, postoperative complications according to the widely used Clavien-Dindo system have added to the register. In **paper IV** complications according to predefined data fields combined with free-text fields and severity grade II or more according to Clavien-Dindo were assessed, and complication rates were 4.0 per cent and 3.8 per cent respectively.

Health-Related Quality of Life measurements

For evaluation of QoL, it is important to select a properly validated questionnaire. QoL instruments can be divided into *generic* or *disease specific*. In **paper II** the general, generic and well-validated SF-36 was used to assess HRQoL in different patient groups before

and after adrenalectomy. In addition, results were compared with results from a large sample of the general Swedish population. There are few studies that evaluate HRQoL after adrenalectomy and thus there is no instrument specifically recommended for the purpose. SF-36 is generally well established, and many clinicians are familiar with the questionnaire.

Ideally, SF-36 should be combined with a disease-specific questionnaire, since generic instruments may not capture symptoms relevant to the disease of interest. Currently, for adrenal tumours, disease-specific questionnaires have only been developed for CS[89, 133].

However, as a pilot for PROMs for SQRTPA, the evaluation was somewhat disappointing, and the module is currently not being used in routine care since it is perceived to be too labour intensive for patients and personnel.

Clinical relevance

In medical research, p values < 0.05 are often considered significant. However, statistical significance does not equal clinical relevance. A clinically important difference may not be statistically significant and therefore ignored in the statistical analysis. In **paper II**, clinical significance was added in addition to the statistical evaluation. Minimally important difference (MID), defined as the smallest change in outcome that a patient may identify, was used to determine clinical importance[134]. However, there is no well-established instrument to assess clinical significance related to SF-36. In **paper II,** clinical significance was defined according to Osoba et al[96]. These authors used the questionnaire QLQ-C30 to evaluate HRQoL in patients with chemotherapy for breast cancer and small-cell lung cancer. Results for QLQ-C30 range from 1 to 100 with 100 as the best outcome. In agreement, in paper II, a difference of 5-10 points was interpreted as a clinically small difference, 10-20 points as a moderate difference and >20 points as a major difference.

Strengths and limitations

Paper	Strengths	Limitations
I	Large national series of patients Well-validated quality register with high coverage Predefined data fields	Retrospective study No general classification of complications Missing data Missing data fields
II	Prospective study HRQoL measured with a well-validated instrument, SF-36 Large reference group Follow-up after 12 months when expected clinical and biochemical stabilization	SF-36 was not supplemented by a disease-specific instrument No evaluation of comorbidity Low response-frequency
III	Well validated and controlled national and quality registries with high coverage On year follow-up Predefined data fields	Retrospective study Only inpatient ICD-codes for evaluation of morbidity by diagnosis Missing data Missing data fields
IV	Large international series of patients Predefined data fields	Retrospective study Different clinical management in different countries Missing data Missing data fields

Conclusions

Evaluation of the national experience of adrenalectomy in Sweden over five years, based on operations registered in SQRTPA, demonstrate that minimally invasive adrenalectomy is widely used with a low risk for complications, low risk for conversion from endoscopic to open surgery and a short hospital stay.

Adrenalectomy seems to be associated with positive effects on HRQoL in patients with benign functional adrenal tumours as evaluated with SF-36. Patients with benign non-functional adrenal tumours reported lower HRQoL before adrenalectomy compared with the general Swedish population, but HRQoL did not improve after adrenalectomy in this patient group, nor patients with malignant tumours.

Based on national and quality register data in Sweden over nine years, hypertension is common in patients with benign adrenocortical tumours regardless of hypersecretion of cortisol or not. The use of antihypertensive drugs is higher for patients with CS, ACS and non-functioning adrenocortical tumours compared with age- and sex-matched controls before adrenalectomy. Adrenalectomy seems to be associated with a positive effect on hypertension in the tumour groups with reduced use of antihypertensive drugs after adrenalectomy.

The results from Eurocrine® 2015-2020 demonstrate that subclinical phaeochromocytoma is common and often present as incidentaloma. A significant proportion of patients with phaeochromocytoma are not treated with preoperative alpha-blockade, with seemingly no negative effects on surgical complications.

Future perspectives

Adrenalectomy is the recommended treatment and cure for several benign and malignant adrenal conditions but is quite often performed as a diagnostic procedure. A firm diagnosis of malignant disease may be difficult to obtain with currently available diagnostic methods. It has also been suggested that patients with adrenal tumours without measurable hormonal hypersecretion, may suffer from increased morbidity.

This thesis shows that minimally invasive adrenalectomy is widely used and is a safe procedure. In **paper I,** the indication for surgery was, among others, suspected malignant disease (suspicious tumour on radiological examination or tumour size >40 mm or preoperatively suspected metastases) in 49 per cent of the patients, but malignant disease was only confirmed on histopathology in 13 per cent of the patients. Open adrenalectomy was performed in 22 per cent of the patients and associated with longer a hospital stay, and conversion was associated with complications. Thus, new diagnostic methods to exclude malignant adrenal tumours is required to be able to reduce the proportion of diagnostic adrenal surgeries and choose proper surgical technique.

Minimally invasive surgery develops in all surgical fields. Surgical outcome after adrenalectomy is excellent no matter which endoscopic technique is used[72], which is also displayed in this thesis. To investigate whether one technique holds an advantage over another technique form part of future studies based on European data in the Eurocrine® database.

The available evidence shows that patients with ACS have a high risk of suffering from sequelae related to cortisol hypersecretion[135]. This has been shown in several observational studies. The effect of adrenalectomy on morbidity is debated but considered favourable for cardiovascular risk factors including diabetes[18, 136, 137]. The results in **paper III** demonstrated a decrease in medication for hypertension after adrenalectomy. To confirm this finding, an international, multicentre randomized controlled trial is currently being performed (Clinical Trials: NCT01246739).

Preoperative treatment with alpha-adrenergic blockade is recommended to prevent haemodynamic instability and cardiovascular events during adrenal surgery for phaeochromocytoma. Some retrospective studies and a meta-analysis indicate that there

may be no need for preparation with alpha-blockade in modern adrenal surgery[39, 40, 129]. The results in the current thesis suggest that an individualized approach may be reasonable. Although an RCT would in theory be optimal, in reality, this may prove difficult due to ethical considerations. Instead, prospective, observational studies, for example through the Eurocrine® database with specific study variables (for instance exact levels of catecholamines, type and dosage of alpha-blockers, hyper- and hypotensive episodes intraoperatively and surgical and medical complications) may be a more reasonable study design.

Svensk sammanfattning

Binjuretumörer är vanliga. De allra flesta binjuretumörer är små och ofarliga och kräver ingen behandling eller uppföljning efter initial utredning. En del binjuretumörer kan dock innebära mer eller mindre svår sjukdom om de inte upptäcks och behandlas i tid.

De senaste 20–30 åren har antalet diagnosticerade binjuretumörer ökat dramatiskt. Det beror på att det görs fler röntgenundersökningar så som datortomografi (CT), ultraljud och magnetkamera (MRI) vid olika sjukdomstillstånd samt mer utvecklad röntgenteknik. Binjuretumörer som hittas av en slump kallas binjureincidentalom och ses hos ungefär en till fyra procent av de personer som genomgått datortomografi av buk eller bröstkorg. Binjureincidentalom är med andra ord ett samlingsnamn på de binjuretumörer som hittats som ett bifynd, men ger ingen ytterligare information om tumörens egenskaper eller sjukdom. Därför krävs vidare utredning för att avgöra om tumören är godartad (benign) eller elakartad (malign) och om den är hormonbildande.

Binjurebarkscancer är en mycket allvarlig sjukdom men samtidigt en relativt sällsynt tumörform. Kirurgi är den huvudsakliga behandlingen som ibland kan bli omfattande med avlägsnande av andra organ förutom cancern. Att avgöra om ett binjureincidentalom är malignt är inte sällan svårt vilket innebär att binjurekirurgi ibland görs som en diagnostisk åtgärd för vävnadsdiagnos.

Majoriteten av godartade binjuretumörer har sitt ursprung i binjurebarken och bildar inga mätbara hormoner, så kallade icke-hormonbildande binjurebarksadenom. En del hormonbildande tumörer upptäcks genom symptom och ger upphov till behandlingskrävande sjukdom. De vanligaste sjukdomarna kopplade till ökad bildning av hormoner är Cushings syndrom (CS) med ökad bildning av kortisol, primär aldosteronism som bildar aldosteron och ger upphov till högt blodtryck och faeokromocytom som bildar adrenalin och noradrenalin vilket innebär risk för mycket högt blodtryck, särskilt vid kroppslig stress.

Även patienter med CS kan lida av högt blodtryck samt diabetes typ II, benskörhet med ökad risk för frakturer och förhöjda blodfetter. Flera av dessa faktorer ökar risken för hjärtkärlsjukdom. Hos ca 5–20 procent av patienter med binjureincidentalom finns ett särskilt tillstånd med lätt ökad hormoninsöndring av kortisol från binjuren men där patienterna saknar typiska symptom på CS, så kallad autonom kortisolsekretion. Det

har visat sig att dessa patienter trots brist på uppenbara symptom har en ökad risk för följdsjukdomar liknande de som finns hos patienter med CS. Intressant nog verkar detta även gälla patienter med icke-hormonbildande binjurebarksadenom. Om binjurekirurgi har en plats i behandlingen av patienter med autonom kortisolproduktion eller patienter med icke-hormonbildande binjurebarksadenom för att minska sjuklighet eller förbättra livskvalitet är ännu ej fastställt.

Antalet binjureoperationer per år har nästan fördubblats i många länder de senaste åren. Detta beror dels på ökat antal binjureincidentalom, men också på operation av tumörer som ger högt blodtryck, screening av patienter med ärftlig sjukdom samt mindre traumatisk operationsteknik där titthålskirurgi underlättar både för patient och kirurg samt förkortar både operationstid och vårdtid.

I denna avhandling utvärderas nyttan av och riskerna med binjurekirurgi för olika sjukdomsgrupper med betoning på risker för komplikationer till kirurgi, patienternas välmående före och efter kirurgi samt förändringar i sjuklighet kopplat till framförallt autonom kortisolsekretion.

För att utvärdera behandlingsstrategier används ofta nationella och internationella kvalitetsregister upprättade för olika sjukdomar och behandlingar. De ger tillgång till omfattande information för ett stort antal patienter. Uppgifter om patienter som ingår i denna avhandling är hämtade från det svenska kvalitetsregistret Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA) (studie I-III) samt Eurocrine® (studie IV), ett europeiskt endokrinkirurgiskt kvalitetsregister.

Riskerna med binjurekirurgi anses vara låga. Få patienter drabbas av komplikationer så som blödning, infektion, blodpropp, skada på andra organ eller död.

I den första studien (I) utvärderades faktorer som påverkar risken för komplikation vid binjurekirurgi, samt faktorer som påverkar risken för att operationen inte går att genomföra som titthålskirurgi utan måste genomföras som öppen kirurgi (så kallad konvertering). Vidare utvärderades faktorer förknippade med lång vårdtid. Resultaten visade att generellt är risken för komplikation låg, 6,5 procent. Den enda riskfaktorn för komplikation var konvertering från titthålskirurgi till öppen kirurgi. Även risk för konvertering var låg, 7,2 procent men med ökad risk vid operation av stor tumör och malign tumör. Medianvårdtiden var 3 dygn och längre hos patienter som hade opererats för två tumörer eller på grund av faeokromocytom samt för patienter som genomgick konvertering till öppen kirurgi vid operation.

Patientens skattning av livskvalitet relaterat till sjukdom eller den behandling patienten får kallas för hälsorelaterad livskvalitet. I den andra studien (II) jämfördes hälsorelaterad livskvalitet före och efter binjurekirurgi hos patienter med binjuretumörer: maligna

eller benigna tumörer samt hormonbildande och inte hormonbildande tumörer. Patienterna fyllde i ett frågeformulär specifikt för bedömning av livskvalitet, kallat SF-36, före samt ett år efter operation. Jämförelser gjordes med befintliga resultat från en representativ andel av Sveriges befolkning. Resultaten visade att patienter med binjuretumör uppvisade sämre livskvalitet jämfört med svenskt normalmaterial före och efter operation men förbättrade dock sin livskvalitet efter kirurgi. Patienter med godartad, hormonellt aktiv tumör hade sämst livskvalitet av alla grupper före operation samt förbättrades mest efter kirurgi. Intressant nog hade patienter med godartad hormonellt inaktiv tumör lika dålig livskvalitet som patienter med malign tumör och ingen av dessa subgrupper av patienter förbättrades i livskvalitet efter operation.

I den tredje studien (III) undersöktes effekten av binjurekirurgi på sjukligheten före och efter binjurekirurgi hos patienter med CS och patienter med en lätt ökad bildning av kortisol i binjuren samt patienter med godartad binjuretumör utan mätbart ökad insöndring av hormoner. De tre patientgrupperna jämfördes med en binjurefrisk kontrollgrupp matchad för ålder och kön. Sjukdomsdiagnoser relaterade till ökade nivåer av kortisol jämfördes före och efter operation liksom utskrivna läkemedel för dessa sjukdomar. Resultaten visade att högt blodtryck var mycket vanligt hos patienter med binjuretumörer oavsett ökad insöndring av kortisol och jämfört med kontroller. Läkemedel för högt blodtryck minskade i alla tumörgrupper successivt årligen efter kirurgi vilket inte skedde i kontrollgruppen. Läkemedel för diabetes och höga blodfetter minskade däremot inte i samma omfattning för patienter med lätt ökad insöndring av kortisol som för patienter med CS. Det var ingen tydlig skillnad för undersökta diagnoser före och efter operation och mellan patient och kontrollgrupperna.

Typiska symptom vid faeokromocytom är svettningar, hjärtklappning och huvudvärk beroende på högt blodtryck. Symptomen kan vara kontinuerliga och milda, men kan även vara plötsliga och utlösas av stress och tryck på tumören. Binjurekirurgi är vedertagen behandling för bot. En betydande andel av patienter med faeokromocytom upptäcks numera inte på grund av symptom utan som binjureincidentalom. En del faeokromocytom diagnosticeras först vid mikroskopisk undersökning av tumören efter kirurgi.

För att minska risken för allvarlig blodtryckshöjning vid operation förbehandlas patienterna med läkemedel som stabilt sänker blodtrycket. Syftet med den fjärde studien (IV) var att studera eventuella typiska symptom, handläggning, förbehandling och kirurgiska resultat med utgångspunkt från hur faeokromocytomet upptäckts hos patienten. Resultaten visade att knappt hälften av faeokromocytomen upptäcktes som binjureincidentalom, 43 procent. Hos 88 procent av patienterna angavs faeokromocytom som orsak till att patienten opererades (operationsindikationen), vilket innebär att diagnosen ställdes innan kirurgi. Trots detta erhöll enbart 90 procent

av dessa patienter förbehandling med blodtryckssänkande läkemedel. Intressant nog verkade vare sig indikation för operation eller eventuell förbehandling påverka risken för kirurgiska komplikationer eller vårdtid.

Sammanfattningsvis visar forskningsresultaten i denna avhandling att binjurekirurgi är säker och förenad med få risker och snabb återhämtning, i synnerhet då operation kan genomföras med titthålsteknik. Vidare visar vi att patienter med binjuretumör har sämre livskvalitet jämfört med normalbefolkningen och en förbättrad livskvalitet efter kirurgi ses enbart hos de patienter som har en ökad bildning av hormoner. Resultaten visar också att högt blodtryck är vanligt hos patienter med godartade tumörer i binjurebarken oavsett om tumören bildar en ökad mängd kortisol eller inte. Operation av binjuren verkar leda till minskad medicinering med blodtrycksmediciner på några års sikt. Så som tidigare visats har patienter med autonom kortisolsekretion en ökad risk även för diabetes och förhöjda blodfetter. Dock sågs ingen säker förbättring efter kirurgi. Framtida kontrollerade studier väntas kunna ge mer entydiga resultat. Risken för kirurgiska komplikationer och lång vårdtid hos patienter som opereras på grund av faeokromocytom påverkas inte av operationsindikationen, inte heller av förbehandling med blodtryckssänkande läkemedel.

Errata

In the original paper I on page 317 in Table 3 and in text the frequency of conversion says 5.6 per cent, it should be 7.2 per cent

In the original paper I on page 317 in Table 2 and in the text on page 316 the minimum tumour size says 1 mm, it should probably be 10 mm

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