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Laparoscopic adrenalectomy in a consecutive series of patients

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Research conducted in the Department of Surgery, Western Infirmary, Glasgow

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Contents

Dedication

To Lucy, Isobel, Elsa and Oliver.

Acknowledgements

Declaration

The work in this thesis was performed at the University Department of Surgery, Western Infirmary, Glasgow.

The work presented in this thesis has been carried out by me except where indicated below:

In Chapter 4, the clearing techniques and histological slides were prepared by N. Galbraith (Department of Anatomy, Glasgow University).

List of Figures

Summary of thesis

Laparoscopic adrenalectomy (LA) has become the procedure of choice for most adrenal pathologies. A number of uncertainties remain which include:

1. The impact of variable adrenal vasculature on LA.

2. The blood supply to the adrenal remnant after subtotal adrenalectomy.

3. Haemodynamic changes during LA for phaeochromocytoma resection.

4. The role of LA for large adrenal tumours (≥6cm).

5. The outcomes of patients undergoing open adrenalectomy (OA) in a series where LA is performed routinely.

6. The role of LA for isolated adrenal metastasis.

The aim of the thesis was to examine these uncertainties using our adrenalectomy series (Jan 1999 – Jan 2009) and anatomical dissection.

We found:

1. The main adrenal vein was remarkably constant and multiple small arteries and veins surround the adrenal gland.

2. During laparoscopic subtotal adrenalectomy, a non functioning adrenal remnant would be unlikely due to an inadequate arterial supply or due to division of the main adrenal vein.

3. LA for phaeochromocytoma was associated with increased episodes of severe intraoperative hypertension (systolic blood pressure 200-220mmHg) when compared to the laparoscopic resection of other adrenal tumours. There were no other significant differences in terms of hypotensive episodes, cardiac arrhythmias or intravenous fluid requirements.

4. In the absence of local invasion, LA for tumours ≥6cm has shown that oncological outcome and post-operative morbidity were comparable to LA for tumours <6cm.

5. In a series where LA was routine, OA was performed infrequently. In the absence of the requirement for an additional open procedure, OA was a demanding procedure associated with resection of adjacent structures and high local recurrence rates.

6. The recovery and oncological outcomes for isolated adrenal metastasis from a renal origin compared very favourably to other series where a more selective policy for laparoscopy was adopted.

1 Introduction

1.1 Adrenal gland anatomy

1.1.1 Macroscopic anatomy

General

The adrenal glands lie directly above the upper poles of the kidneys. They are surrounded by perinephric fat and enclosed within their own compartment of the renal fascia. The glands are recognizable by their golden yellow appearance.

Right adrenal gland

The right gland is pyramidal in shape. The anatomical relationships are illustrated in Figure 1.1. The anterior surface is overlapped by the inferior vena cava (medially) and the bare area of the liver. It lies on the diaphragm, with its base directly above the upper pole of the right kidney.

Left adrenal gland

The left adrenal gland is said to look like a workman's cap. The blood supply and some of the anatomical relationships are illustrated in Figure 1.1. The anterior surface is overlapped by the peritoneal wall of the lesser sac and the distal pancreas and splenic artery (inferiorly). It lies on the left crus of the diaphragm, draped over the medial border of the left kidney.

Figure 1.1 Diagram showing the blood supply and position of the adrenal glands in relation to the aorta, inferior vena cava and kidneys
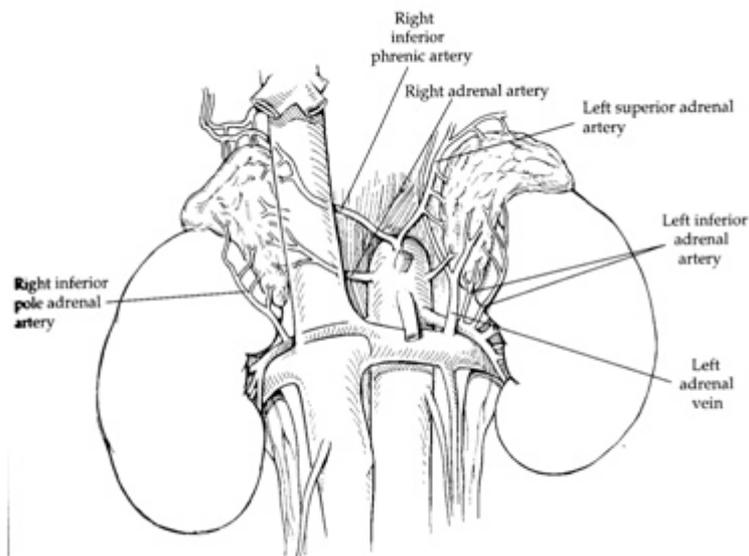
Adrenal gland blood supply

The adrenal gland is supplied by multiple small arterial branches which ramify over the adrenal capsule. The arterial branches originate from three sources: the inferior phrenic artery, the aorta and the renal arteries (Gray & Williams, 1989)

The drainage of the adrenal gland is usually by a single vein: the right adrenal vein into the inferior vena cava and the left adrenal vein into the left renal vein. The main right adrenal vein may only be a few millimetres (Gray & Williams, 1989) (Sinnatamby & Last, 1999).

Any variability of adrenal gland vasculature is not clear from standard anatomy texts (Sinnatamby & Last, 1999) (Gray & Williams, 1989). Nor is it clear, in the presence of adrenal pathology, if venous variability or the number of arterial branches would increase. This could have implications in terms of bleeding complications during adrenalectomy or to the blood supply of the adrenal remnant when performing a subtotal adrenalectomy. We felt the

magnified view of laparoscopy (2.5-3 times normal) may allow a more accurate view of the vasculature compared to the traditional open techniques for adrenal pathologies.

1.1.2 Microscopic anatomy

The adrenal gland is separated into the adrenal cortex (yellow colour) and medulla (grey colour). The gland is surrounded by a capsule composed of collagen.

The adrenal cortex is divided into three zones: the outer glomerulosa, the intermediate fasciculata and the inner reticularis. These three zones produce mineralocorticoids, glucocorticoids and sex steroids respectively.

The adrenal medulla consists of groups of chromaffin cells (phaeochromocytes) separated by venous sinusoids. Chromaffin cells synthesize, store and release catecholamines (epinephrine, norepinephrine) into the venous sinusoids.

Paraganglia are extra-adrenal aggregations of chromaffin tissue which tend to be distributed near or in the autonomic nervous system.

1.2 Adrenal physiology

1.2.1 Adrenal cortex

The hormones of the adrenal cortex are derivatives of cholesterol. The three hormone classes secreted in physiological significant amounts are:

Glucocorticoids (produced from the zona glomerulosa): cortisol is the major glucocorticoid in humans

Mineralocorticoids (produced from the zona fasciculata): aldosterone is the major mineralcorticoid

Androgens (produced from the zona reticularis): dehydroepiandrosterone and androstenedione

Of these three hormone classes, the only one essential for life is glucocorticoids.

Glucocorticoids

The negative feedback control of cortisol secretion is illustrated by the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1.2). Plasma cortisol level is controlled by the sum of neural factors acting on the hypothalamus and the effect of negative feedback of cortisol action on the anterior pituitary gland and hypothalamus. The effects of glucocorticoids are summarised in Table 1.1.

Figure 1.2 Control of the hypothalamic-pituitary-adrenal axis
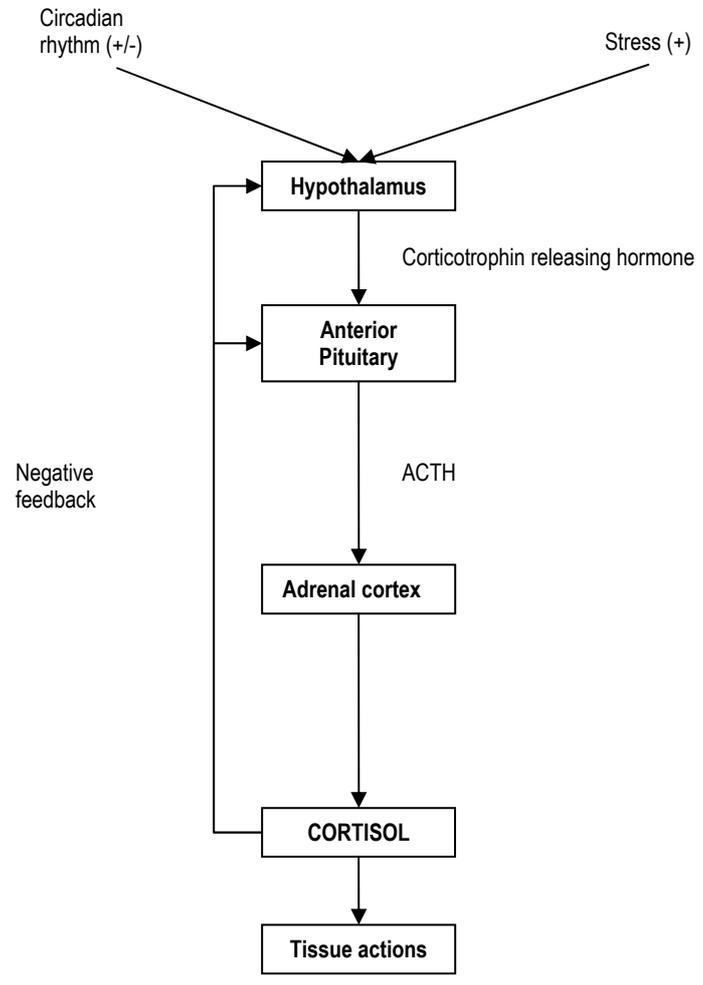
Table 1.1 Action of glucocorticoids

Action	Increase plasma glucocorticoids	Decrease plasma glucocorticoids
Metabolism	Protein catabolism Hepatic glycogenesis	Protein synthesis Hepatic glycogenolysis

	Hepatic gluconeogenesis Lipolysis	
Vascular	Vascular tone	Impair vascular tone
Immunological	Immunosuppression	
Inflammatory	Inhibit the inflammatory response to injury	
Nervous system	Behaviour and mood effects	
Bone	Bone dissolution	Bowel absorption of calcium

Cushing's syndrome is the term given to prolonged exposure to excessive glucocorticoids. Typical clinical findings would include: moon face, truncal obesity, hirsutism, hypertension and easy bruising. This can be endogenous or exogenous. Exogenous causes are the most common. This is often due to the iatrogenic administration of glucocorticoids for chronic medical pathologies.

For endogenous Cushing's syndrome the causes can be divided into ACTH-dependant and ACTH-independent. Table 1.2 illustrates the common causes of excessive glucocorticoid production. The most common cause of endogenous Cushing's syndrome is Cushing's disease. Occasionally, bilateral adrenalectomy is indicated for select patients with persistent Cushing's disease. This includes failure following pituitary resection. Adrenalectomy is usually indicated for ACTH-independent Cushing's syndrome.

Table 1.2 Endogenous causes of Cushing's syndrome

ACTH-dependant Cushing's disease (pituitary adenoma) Ectopic ACTH syndrome (eg lung cancer)
ACTH-independent Adrenal adenoma Adrenocortical carcinoma (rare) Primary pigmented nodular adrenal dysplasia (rare)
ACTH-variable Macronodular hyperplasia (rare)

Mineralocorticoids

Aldosterone secretion is regulated by a number of factors: renin-angiotensin system in a feedback mechanism, ACTH from the pituitary gland and direct stimulatory effect on the adrenal cortex by a rise in plasma potassium or decrease in plasma sodium.

Aldosterone increases the reabsorption of sodium from the kidneys and excretion of potassium and hydrogen. Excessive secretion of aldosterone leads to hypokalaemia and an increase in the extracellular volume with resultant hypertension.

Excessive aldosterone production can be primary or secondary. Secondary aldosteronism is caused by elevated renin and angiotensin II levels. This results from a low effective arterial blood volume. Examples include: congestive cardiac failure, liver cirrhosis and nephrosis. The causes of primary aldosteronism are listed in Table 1.3. The most common cause is an aldosterone-producing adrenocortical adenoma (Conn's syndrome). It is important to differentiate between idiopathic hyperaldosteronism and Conn's adenoma. Unilateral adrenalectomy is curative for Conn's adenoma but not for the other.

Table 1.3 Aetiology of primary aldosteronism

Aetiology	Percent
Aldosterone producing adrenocortical adenoma (Conn's syndrome)	65%
Idiopathic hyperaldosteronism with bilateral adrenal hyperplasia	25%
Primary adrenal hyperplasia	5%
Renin-responsive aldosterone-producing adenoma	5%
Adrenocortical carcinoma	rare

Androgens

Secretion of androgens is under the control of ACTH from the pituitary gland. The main effects of androgen secretion are: masculinizing effects, promotion of protein anabolism and growth. Adrenal androgens cause very little masculinizing effects when secreted in normal amounts. However, when secreted in excessive amounts can cause severe masculinization. In males this can lead to precocious pseudopuberty and in females adrenogenital syndrome.

Adrenocortical insufficiency

Adrenocortical insufficiency is due to inadequate secretion of glucocorticoid and mineralcorticoid hormones. Adrenal insufficiency can be primary or secondary. Primary adrenal insufficiency occurs when there is direct destruction of the adrenal glands. This is usually due to Addison's disease (autoimmune related adrenal atrophy). Secondary adrenal insufficiency results from an impairment of ACTH secretion due to pituitary or hypothalamic disorders.

Addisonian crisis may occur in this group of patients following acute withdrawal of steroids, severe sepsis or trauma. Mainstay of treatment would be fluid resuscitation and hydrocortisone administration.

1.2.2 Adrenal medulla

The adrenal medulla secretes catecholamines from the chromaffin cells. The catecholamines are: norepinephrine, epinephrine and dopamine. In humans, most catecholamine output is epinephrine.

Catecholamines

Catecholamine secretion from the adrenal medulla is under neural control. Increased adrenal catecholamine secretion is part of the diffuse sympathetic discharge in emergency situations. This is termed the emergency function of the sympathoadrenal system. It is a way for preparing individuals for fight or flight. The effects of catecholamines are shown in Table 1.4.

Table 1.4 Actions of catecholamines

	Catecholamine	Effect
Metabolism	NE, E	Increase glycogenolysis Mobilisation of fat Rise in metabolic rate
Cardiovascular β_1 receptors β_2 receptors α_1 receptors	 NE, E, dopamine E NE	 Increase force and rate of contraction Dilates blood vessels in skeletal muscle Produces vasoconstriction in all organs

NE= norepinephrine, E= epinephrine

Abnormal elevated levels of catecholamine can result from tumours that arise from adrenal chromaffin cells. These are called phaeochromocytomas. Classic symptoms and signs include: episodic headaches, palpitations and sweating associated with sustained or paroxysmal hypertension (Werbel & Ober, 1995). Adrenalectomy is the treatment of choice for sporadic or hereditary unilateral phaeochromocytoma. For patients with inherited syndromes with bilateral phaeochromocytomas bilateral or cortex-sparing adrenalectomy must be considered (Petri, van Eijck, de Herder, Wagner, & de Krijger, 2009).

1.3 Clinical presentation

Clinical presentation can often be non-specific or the patient can present after incidental adrenal gland imaging.

1.3.1 Conn's syndrome

The symptoms and signs are non-specific and include hypertension and hypokalaemia.

1.3.2 Cushing's syndrome

Symptoms and signs include: truncal obesity, decreased libido, thin skin, hypertension, hirsutism, depression, easy bruising, glucose intolerance and general weakness.

1.3.3 Phaeochromocytoma

Phaeochromocytoma is suspected in patients with: episodic episodes of headaches, sweating and palpitations with poorly controlled persistent or intermittent hypertension.

1.3.4 Incidentaloma

Adrenal incidentaloma is an adrenal tumour (≥1cm) discovered on an imaging study for other unrelated pathologies. Over the last one and a half decades incidental adrenal gland imaging is increasingly performed as computed tomography for other abdominal pathologies has become common. This has led to an increase in patients with an incidental adrenal tumour referred for surgical and endocrine assessment (Saunders et al., 2004). Presently between 4-6% of the imaged population have incidentalomas (Bovio et al., 2006)(Kloos, Gross, Francis, Korobkin, & Shapiro, 1995). Almost all these lesions will be benign in a patient without a known history of cancer (Song, Chaudhry, & Mayo-Smith, 2007)(Young, 2000).

1.4 Assessment of adrenal tumours

Adrenal tumours are characterised by radiological and hormonal assessment.

1.4.1 Radiological assessment

The main modalities of choice in the evaluation of an adrenal tumour are computed tomography (CT) or magnetic resonance imaging (MRI). Most investigators use CT as the initial modality of choice as it is more readily available and cheaper. Occasionally when CT or MRI studies are inconclusive patients are referred for combined positron emission tomography and computed tomography (PET-CT).

Adrenal tumours can be characterized using imaging alone. Characterisation of the adrenal tumour depends on a number of factors which include: morphology, perfusion differences and intracellular lipid concentration (Boland, Blake, Hahn, & Mayo-Smith, 2008).

Morphology appearances which may suggest malignancy include: increased size, large necrotic areas, increased heterogeneity, irregular borders and local invasion. Available data suggests, at a size threshold of ≥4cm the likelihood of malignancy doubles and is more than ninefold higher for tumours ≥8cm (Sturgeon, Shen, Clark, Duh, & Kebebew, 2006).

Lipid sensitive imaging by CT or MRI exploit the fact that most adenomas contain abundant intracellular fat where as almost all malignant lesions do not (Korobkin et al., 1996). It has been reported an unenhanced CT densitometry technique can effectively differentiate many adrenal adenomas from malignant adenomas. Figure 1.3 shows a typical adrenal adenoma from an unenhanced CT. If the CT attenuation threshold is set at 10 hounsfield units the sensitivity and specificity for characterising adenomas versus non-adenomas has been reported 71% and 98% respectively (Boland et al., 1998). This method has limitations which include: up to 30 % of adenomas are lipid poor and most CT scans for other pathologies are contrast enhanced (Boland et al., 2008). Therefore, using attenuation values in these cases would be considered indeterminate or difficult to interpret.

More recently studies have reported improved results using CT perfusion washout scans or chemical shift MR imaging. For CT, an initial non-contrast or contrast enhanced scan is performed followed by a contrast enhanced examination after a variable delay (often 15 minutes). Benign lesions typically demonstrate more than 50% washout. A threshold enhancement washout value is then calculated. Chemical shift MR imaging utilises the different resonant frequencies of fat and water protons. Benign lesions typically show signal intensity decrease when compared with in-phase images. Figure 1.4 illustrates axial MRI images of an 11cm adrenal mass. The size and unchanged signal intensity makes this highly suspicious of malignancy. Histology confirmed the suspicion. From the available data, CT perfusion washout scan appears to offer the highest sensitivity and specificity for adrenal adenoma characterization (Park, Kim, Kim, & Lee, 2007).

PET-CT allows adrenal lesion morphology and metabolic activity to be coregistered on the same image. This would allow a more accurate anatomic localization of any PET abnormalities. In current practice patients would only be referred for PET-CT rarely if CT or MR results are inconclusive (Boland et al., 2008).

[123] I-MIBG is concentrated in catecholamine storage vesicles. A meta-iodobenzylguanidine (MIBG) scan can help identify phaeochromocytoma, extra-adrenal phaeochromocytoma and metastatic deposits from the phaeochromocytoma.

Despite the above techniques, the only reliable imaging findings to differentiate between malignant and benign adrenal tumours remain the presence of regional invasion or metastatic disease. Figure 1.5 shows an MR scan of a locally invasive adrenal mass.

Figure 1.3 Unenhanced CT of a left adrenal adenoma (arrow)

Figure 1.4 Axial MR images of a large right adrenocortical carcinoma. **(a)** T1-weighted in-phase image shows signal intensity (long arrow) similar to spleen (short arrow). **(b)** T1 weighted opposed phase image shows unchanged signal density

a,

b,
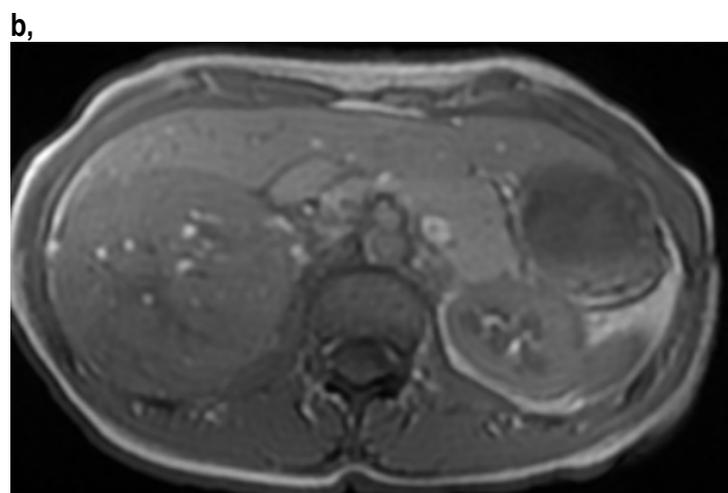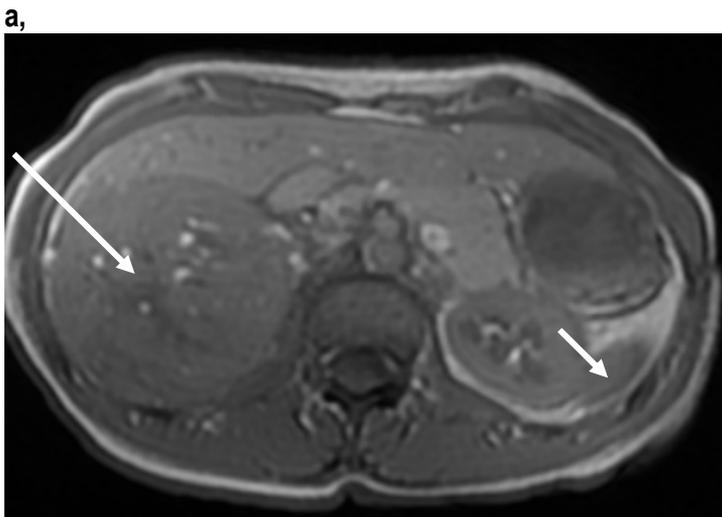
Figure 1.5 MR image of a locally invasive adrenocortical carcinoma (long arrow). **(a)** Coronal slice showing invasion into kidney (short arrow). **(b)** Tumour thrombus into inferior vena cava (arrow).

a,

b,
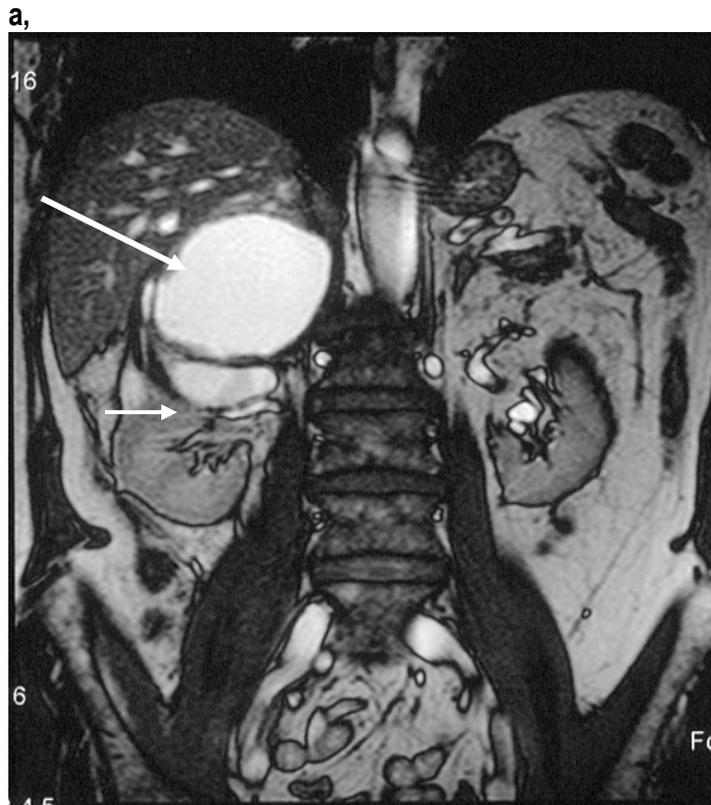
1.4.2 Hormonal assessment

All adrenal tumours require hormone evaluation. The hormone studies are performed to check for: phaeochromocytoma, Cushing's syndrome and Conn's syndrome.

A phaeochromocytoma screen included a 24 hour urine collection for catecholamines (norepinephrine, epinephrine and dopamine) and metabolites (metanephrine, normetanephrine, vanillylmandelic acid). Cushing's syndrome/disease assessment included 24 hour urinary cortisol, serum cortisol and plasma ACTH, low dose dexamethasone suppression test and plasma androgen measurements. A Conn's syndrome screen included urea and electrolytes, plasma renin and aldosterone levels. Adrenal vein sampling can be used for patients with suspected Conn's syndrome when imaging does not demonstrate an obvious adenoma.

1.4.3 Adrenal biopsy

Ultrasound or computed tomography guided fine needle aspiration (FNA) is unhelpful to distinguish between benign and malignant adrenal tumours due to the high false negative rate (Sasano, Shizawa, & Nagura, 1995). The only potential use of FNA is to help diagnose metastasis when adrenal resection is not planned and detection would alter patient management (Lee et al., 1998).

1.5 Indications for adrenalectomy

Adrenalectomy is indicated for all hormonally active adrenal lesions, suspicion of adrenal malignancy on imaging (size ≥4cm, local invasion, tumour heterogeneity, high attenuation and irregular tumour margins) and isolated adrenal metastases.

Management of a non functioning adrenal lesion remains debatable. All authors advocate resection of large ≥6cm non functional adrenal tumours due to the increased risk of malignancy. No prospective controlled studies exist for the role of adrenalectomy for adrenal masses of 3-6 cm. Different authors have advocated size tumour thresholds of 3,4,5 and 6cm for resection of non functioning adrenal tumours (Duh, 2002)(G. B. Thompson & Young, 2003)(Eldeiry & Garber, 2008). Sturgeon et al characterized the relationship between tumour size and malignancy risk compared the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database for adrenocortical carcinoma with their own experience with benign adrenal cortical adenomas from a similar time period. From the SEER database 457 adrenal cortical carcinomas were identified (376 had size data) and 47 patients from their own series with benign adrenal cortical adenomas. The authors found a tumour threshold of 4cm has a sensitivity and specificity of 96% and 52% for malignancy versus 90% and 80% for a tumour threshold of 6cm. The authors advocated that all tumours ≥4cm should be surgical resected (Sturgeon et al., 2006).

In the current series indications for adrenalectomy included: all hormonally active adrenal lesions, all tumours ≥ 4cm, suspicion of adrenal malignancy on imaging (local invasion, tumour heterogeneity, high attenuation and irregular tumour margins) and isolated adrenal metastases. Resection of non functioning adrenal tumours <4cm was indicated for patients with evidence of tumour growth on serial radiological imaging. The only contraindications to laparoscopy were locally invasive adrenal carcinoma (laparoscopic en-bloc nephrectomy was performed after

2007 if there was isolated local invasion to the kidney) or the requirement of an additional open

surgical procedure.

1.6 Perioperative management

1.6.1 Bilateral adrenalectomy

Bilateral adrenalectomy can be indicated following relapse after pituitary surgery, bilateral adrenal hyperplasia or hereditary phaeochromocytoma. Perioperative intravenous hydrocortisone is required to prevent acute adrenal insufficiency. When oral intake has been established lifelong oral steroids are required. Increased doses are required at times of stress (eg trauma, infection).

1.6.2 Autonomous cortisol secretion

For patients with autonomous cortisol secretion after hormonal testing a perioperative 'stress dose' of hydrocortisone is recommended. A post operative in-patient short SYNACTHEN test would follow. If the test indicates adrenal insufficiency (low level of stimulated cortisol) steroid replacement should continue as this indicates HPA axis suppression. Patients are then reviewed as an out-patient to test for HPA axis recovery. If the test indicates adequate cortisol response (functioning HPA axis) steroid replacement therapy can stop.

1.6.3 Phaeochromocytoma

The perioperative medical management of patients with phaeochromocytomas is essential to reduce the effects of circulating catecholamines (Plouin, Duclos, Soppelsa, Boublil, & Chatellier, 2001)(Kinney et al., 2000). These can include severe hypertension (systolic blood pressure >200mmHg), tachycardia, arrhythmias and death. Immediate surgery is rarely essential.

Medical management aims to control blood pressure, heart rate and arrhythmias. Traditional preoperative regimens have included phenoxybenzamine (a long-acting non-selective alpha blocker) and propanolol (beta blocker) (Ross, Prichard, Kaufman, Robertson, & Harries, 1967). Other agents have been used effectively including selective alpha blockers and calcium

channel antagonists (Prys-Roberts & Farndon, 2002)(Lebuffe et al., 2005). No trial exists comparing the traditional regimen with other medical managements.

Despite preoperative medical management, intraoperative tumour manipulation or introduction of pneumoperitoneum (laparoscopic adrenalectomy) may cause severe haemodynamic responses requiring further treatment with short acting alpha blockers (eg phentolamine) or short acting beta blockers (eg labetalol) (Joris et al., 1999)(Tauzin-Fin, Sesay, Gosse, & Ballanger, 2004).

In the current series, we used a preoperative phenoxybenzamine regimen (fully described in Chapter 5) and felt complete alpha blockade was achieved in all cases. Preoperative beta blockade was not routinely administered. As a result, we felt using this regimen and a specialist endocrine, anaesthetic and surgical team the perioperative haemodynamic stability of laparoscopic adrenalectomy (LA) for phaeochromocytoma has improved to such a degree that they may now be comparable to LA for other non-catecholamine secreting adrenal tumours.

1.7 Adrenal gland pathology

Adrenal tumours can be divided into those arising from the adrenal cortex, those arising from the adrenal medulla, those arising from other components of the adrenal gland or those that metastasize to the adrenal gland.

1.7.1 Adrenocortical tumours

Tumours arising from the adrenal cortex include adenomas and carcinomas. Adrenal cortical adenomas can be hormonally active or hormonally inactive. Hormonally active adenomas are classified according to the hormone secreted. Aldosterone producing adenoma is termed Conn's syndrome or primary aldosteronism. Cortisol producing adenoma and is termed Cushing's syndrome (ACTH-independent). Macronodular adrenal hyperplasia can also cause an ACTH-independent Cushing's syndrome. These patients may require bilateral adrenalectomy. Cushing's disease is glucocorticoid excess caused by a pituitary adenoma (ACTH-dependent). In some circumstances bilateral adrenalectomy is required due to persistent hypercortisolism after failed neurosurgical intervention.

Hormonally inactive adenomas are termed non-functioning adrenal cortical adenomas or adrenal incidentalomas. These are usually detected when radiological imaging was performed for other pathology.

On histopathological examination it is not generally possible to differentiate between the functional types of adenoma. This is dependant on prior hormone assessment.

1.7.2 Adrenal cortical carcinoma

Adrenal cortical carcinoma is a rare malignant epithelial tumour of adrenal cortical cells (incidence about one case per million population per year) (Gicquel, Baudin, Lebouc, & Schlumberger, 1997)(Dackiw, Lee, Gagel, & Evans, 2001). About 80 % of the tumours are functional (mainly glucocorticoid or androgen excessive secretion). Distinguishing adrenal cortical carcinoma from adrenal cortical adenomas can be difficult. There are a number of

classifications predicting malignant behaviour. A modification of the Weiss criteria has been the most widely used. This is based on nine histopathological criteria:

1. High nuclear grade

2. >5 mitoses per 50 high-power fields

3. Atypical mitotic figures

4. <25% of tumour cells are clear cells

5. Diffuse architecture (>33% of tumour)

6. Necrosis

7. Venous invasion (smooth muscle in wall)

8. Sinusoidal invasion (no smooth muscle in wall)

9. Capsular invasion

The presence of three or more criteria highly correlates with subsequent malignant behaviour (Weiss, 1984)(Aubert et al., 2002).

1.7.3 Phaeochromocytoma

A phaeochromocytoma is a tumour of chromaffin cells of the adrenal medulla (Figure 1.6). Most phaeochromocytomas are sporadic. However, increasing evidence suggests up to 24% of patients have a hereditary basis for phaeochromocytoma (Bauters et al., 2003). Genetic syndromes at increased risk of phaeochromocytoma include: multiple endocrine neoplasia type 2, von Hippel Lindau syndrome or neurofibromatosis type 1. Phaeochromocytomas are usually associated with excess production of catecholamines. Excess catecholamine production is detected by measurement of increased levels of urine or plasma concentration of catecholamines or their metabolites.

Malignant phaeochromocytomas are defined by the presence of metastatic disease. This definition does not account for those tumours with malignant potential. Therefore, a series of histological criteria such as vascular invasion, atypical mitotic figures or capsular invasion have

been identified to detect those patients with potentially malignant phaeochromocytomas (van der Harst et al., 2000)(L. D. Thompson, 2002)(Linnoila, Keiser, Steinberg, & Lack, 1990). However, several studies evaluating the criteria have reached differing conclusions. Unless metastatic disease is present, it is only possible to report the malignant potential. Therefore, until a test can accurately predict malignant behaviour all patients should be followed lifelong for hormonal assessment and repeat imaging to detect metastatic disease or local recurrence.

Figure 1.6 Transverse section of a large phaeochromocytoma (scale in cm)

1.7.4 Adrenal soft tissue and germ cell tumours

These tumours can be benign or malignant arising from components of the adrenal gland other than steroid producing or catecholamine producing cells. Benign tumours include myelipoma, haemangioma, leiomyoma, schwannomas, ganglioneuromas or teratomas. Malignant tumours include leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumours and melanoma.

1.7.5 Adrenal metastases

Adrenal metastases are defined as tumours that originate in extraadrenal locations and spread to the adrenal gland by metastasis. The most common primary sites were breast, lung, kidney, stomach, pancreas, ovary and colon. Adrenalectomy may prolong survival in a highly selective group of patients with solitary adrenal metastatic disease (Kim, Brennan, Russo, Burt, & Coit, 1998b)(Paul, Virgo, Wade, Audisio, & Johnson, 2000). This has been reported for patients with adrenal metastases originating from colorectal carcinoma, lung carcinoma, renal carcinoma and melanomas. The role of LA for these patients is controversial as some authors feel a preoperative diagnosis of malignancy is a contraindication to laparoscopy.

1.8 Adrenalectomy

1.8.1 Open versus laparoscopic adrenalectomy

Open adrenalectomy (OA) either by the transabdominal, thoracoabdominal or lumbar approach can cause a number of post operative problems. These include: pain, respiratory complications or prolonged hospital stay. Following the success of laparoscopic cholecystectomy, laparoscopic adrenalectomy (LA) was first introduced in an attempt to reduce the morbidity associated with the open procedure. LA was first described by Gagner et al in 1992 (Gagner, Lacroix, & Bolt, 1992). They described a successful anterior transabdominal approach in 3 patients (Cushing's syndrome, Cushing's disease and a phaeochromocytoma). The authors felt that LA may reduce morbidity, reduce analgesic requirements and reduce post operative stay when compared to OA.

Since this time, multiple case-control studies have consistently demonstrated the benefits of LA compared OA in terms of blood loss, analgesic requirements, post operative complications, hospital stay and earlier return to normal activity for a variety of adrenal gland pathologies. Table 1.5 gives an overview of outcomes for studies comparing LA versus OA.

Table 1.5 Outcomes for laparoscopic adrenalectomy versus open adrenalectomy

Author	Year	No. of patients		Blood loss (mls)*		Analgesia requirements	Complications (%)		Length of stay (days)*	
		LA	OA	LA	OA	(LA versus OA)	LA	OA	LA	OA
(Brunt et al., 1996))	1996	24	42	104	387	Reduced analgesia requirement	17	64	3.2	7.5
(MacGillivray, Shichman, Ferrer, & Malchoff, 1996)	1996	17	12	198	500	n.a	21	56	3	7.9
(Staren & Prinz, 1996)	1996	21	20	n.a.		n.a.	n.a.		2.2	6.1
(G. B. Thompson et al., 1997)	1997	50	50	n.a.		Reduced analgesia requirement	6	72	3.1	5.7
(Jacobs, Goldstein, & Geer, 1997)	1997	19	19	109	263	n.a.	5	38	2.3	5.1
(Linos et al., 1997)	1997	18	147	n.a.		Reduced duration of PCA use	0	12	2.2	6.3
(Vargas et al., 1997)	1997	20	20	245	283	Reduced analgesia requirement	10	25	3.1	7.2
(Winfield, Hamilton, Bravo, & Novick, 1998)	1998	21	17	183	266	Reduced analgesia requirement	29	76	2.7	6.2
(Ting, Lo, & Lo, 1998)	1998	12	56	50	150	Reduced analgesia requirement	0	9	3	5
(Imai, Kikumori, Ohiwa, Mase, & Funahashi, 1999)	1999	40	40	40	172	Reduced analgesia requirement	5	50	12	18
(Dudley & Harrison, 1999)	1999	36	23	n.a.		n.a.	6	52	3.5	8.5
(Soares, Monchik, Migliori, & Amaral, 1999)	1999	12	7	132	278	Reduced analgesia requirement	8	0	2.1	5.4
(Schell, Talamini, & Udelsman, 1999)	1999	22	17	n.a.		n.a.	n.a.		1.7	6.7
(Shen et al., 1999)	1999	42	38	n.a.		n.a.	0	11	n.a.	
(Rayan & Hodin, 2000)	2000	19	48	n.a.		n.a.	3	60	1.5	6.3
(Hazzan et al., 2001)	2001	24	28	n.a.		Reduced analgesia requirement	16	39	4	7.5
(Ortega, Sala, Garcia, & Lledo, 2002)	2002	10	10	n.a.		n.a.	10	30	3.7	5.8

*Values are mean. LA, laparoscopic adrenalectomy;OA, open adrenalectomy;PCA, patient controlled analgesia;n.a., data not available

Despite the lack of Level 1 evidence comparing LA with OA, it seems unlikely randomized controlled trials will be performed. This is primarily due to the benefits consistently demonstrated in favour of LA.

Therefore, LA has become the procedure of choice for most adrenal gland pathologies.

1.8.2 Laparoscopic operative technique

Laparoscopic approaches to the adrenal gland include the retroperitoneal approach, anterior transabdominal approach or the lateral transabdominal approach.

The retroperitoneal approach was first described in 1995 (Mercan, Seven, Ozarmagan, & Tezelman, 1995) and subsequent series have since reported a safety and efficacy comparable to other laparoscopic approaches (Hanssen et al., 2006)(Bonjer et al., 2000)(Walz et al., 2006). Drawbacks to this approach include lack of familiarity amongst most general surgeons, limited working space and the unsuitability for resection of large adrenal tumours (≥6cm). Potential advantages are avoidance of the peritoneal cavity in patients with previous upper gastrointestinal surgery. From available studies, patient outcome remains similar compared to the lateral transabdominal approach for small-medium sized tumours.

The anterior transabdominal approach is practised infrequently and therefore the evidence favouring this approach is scarce. The main reason for its unpopularity is the increased dissection, adjacent structure retraction difficulties and longer operating times compared to other procedures.

The lateral transabdominal approach is the most popular approach in published case series. Reasons include: easiest to learn due to presence of an increased number of anatomical landmarks compared to the retroperitoneal approach and the ability to perform large adrenal tumour (≥6cm) resection. This was the favoured approach in the current series. This technique, initially described by Gagner, is described in detail.

1.8.3 Lateral transabdominal laparoscopic adrenalectomy

Patient positioning

The patient placed is in the lateral decubitus position with the operative side up. The table is broken to increase the space between the costal margin and iliac crest.

Left side

The port placements are illustrated in Figure 1.7. The middle port (10mm) is for a 30° camera and inserted using an open technique at a point just lateral to the rectus at the level of the umbilicus. Two instrument ports (5mm,5mm) are inserted under direct vision. One 5mm port is inserted parallel to the costal margin in the mid-clavicular line. The other 5mm port is inserted under the eleventh rib in the mid-axillary line. A further 5mm port is occasionally required to assist with splenic retraction. The splenic flexure of the colon and the lienorenal ligament of the spleen are mobilised using ultrasonic dissection. The colon can then be displaced inferiorly and the spleen displaced medially (Figure 1.8). This allows access to the adrenal gland. Dissection starts at the infero-medial aspect to allow early visualisation of the left adrenal vein (Figure 1.9). This is then divided between clips. The adrenal gland together with its surrounding fat are mobilised using ultrasonic dissection or electrocautery taking care not to breach the adrenal gland capsule. The adrenal gland is then removed via the camera port using a retrieval bag. The wound may require extension to allow retrieval.

Figure 1.7 Port sites for left laparoscopic adrenalectomy. A 10 mm camera port and two (5mm) instrument ports are used

Instrument port (5mm)

Camera port (10mm)

Instrument port (5mm)

38
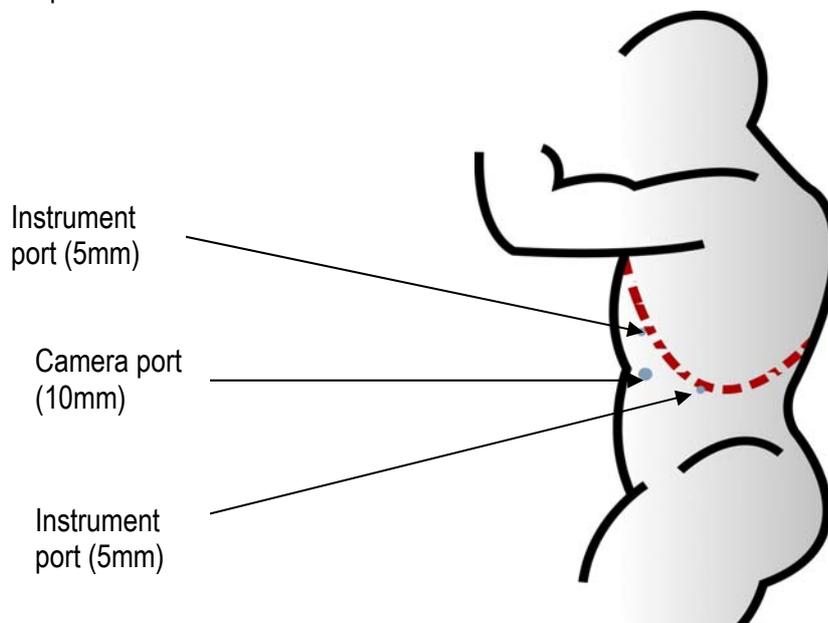
Figure 1.8 The lateral attachments of the spleen is mobilised allowing it to be displaced medially allowing access to the adrenal gland and adrenal vein

Spleen

Adrenal gland

Lienorenal ligament

Kidney
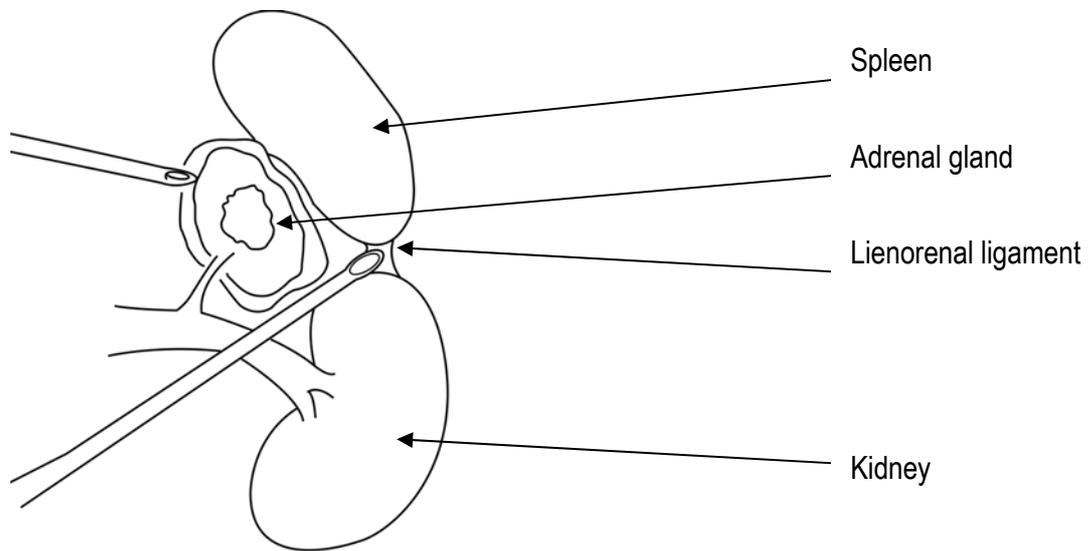
Figure 1.9 The left adrenal vein is treble clipped and divided with harmonic scalpel. The adrenal gland is then completely mobilised

Left adrenal gland

Left adrenal vein

Clip applicator
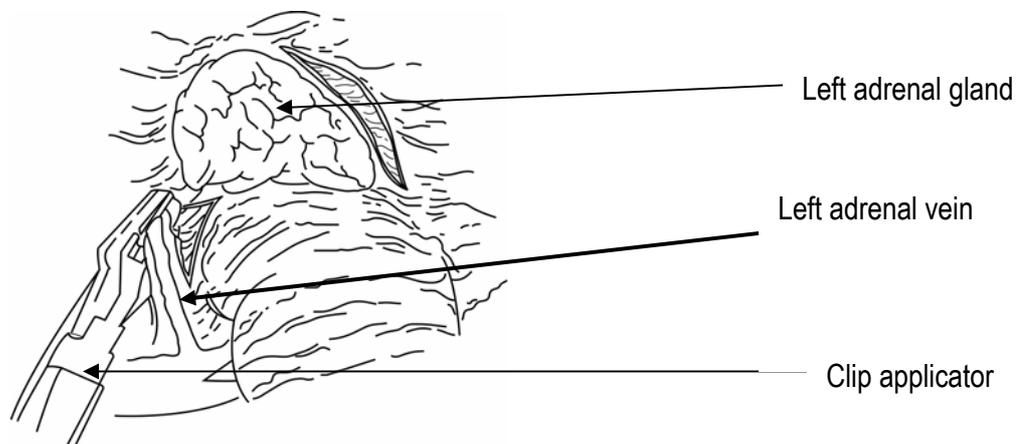
Right side

The port placements are illustrated in figure 1.10. The camera port (10mm) is inserted just lateral to the rectus at the level of the umbilicus (30° laparoscope). Two 5mm instrument ports are placed as for the left side and a third is placed in the right iliac fossa. The most medial port is used to retract the right liver lobe. The right lobe of liver is mobilised from its lateral and posterior attachments and retracted (figure 1.11). This allows access to the adrenal gland and inferior vena cava. The lateral border of the inferior vena cava is dissected from the inferior part of the liver to the origin of the right renal vein. The main adrenal vein will be located between these points. After careful dissection the adrenal vein is divided between clips (figure 1.12). Care should be taken to ensure there is no duplicate adrenal vein. The adrenal gland together with its surrounding fat is then mobilised using ultrasonic dissection or electrocautery. The adrenal gland is removed via the camera port using a retrieval bag. The adrenal gland was not morcellated.

Figure 1.10 Positioning and port placement for right laparoscopic adrenalectomy. On the right side a third instrument port (5mm) is used to allow liver retraction
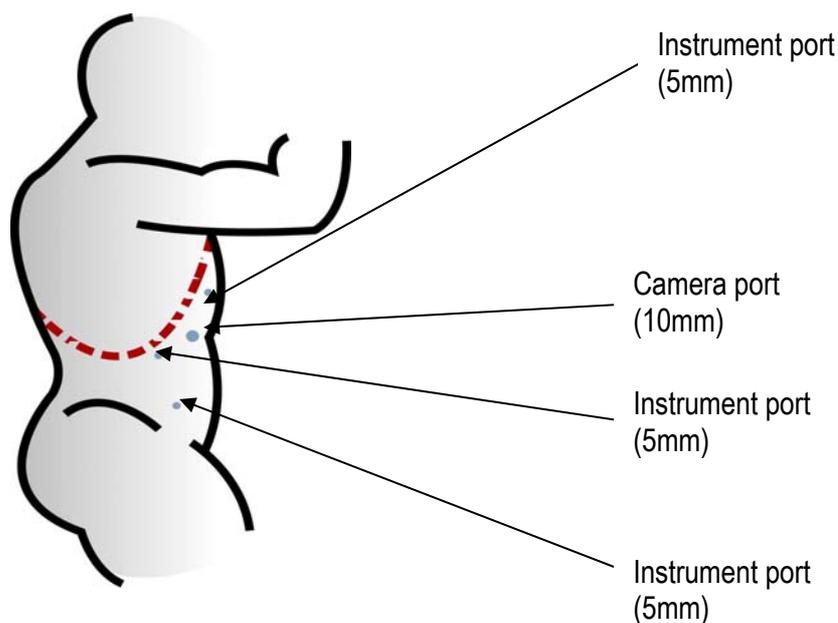
Figure 1.11 The lateral attachments of the liver (arrow) are been divided to allow medial and

superior mobilisation
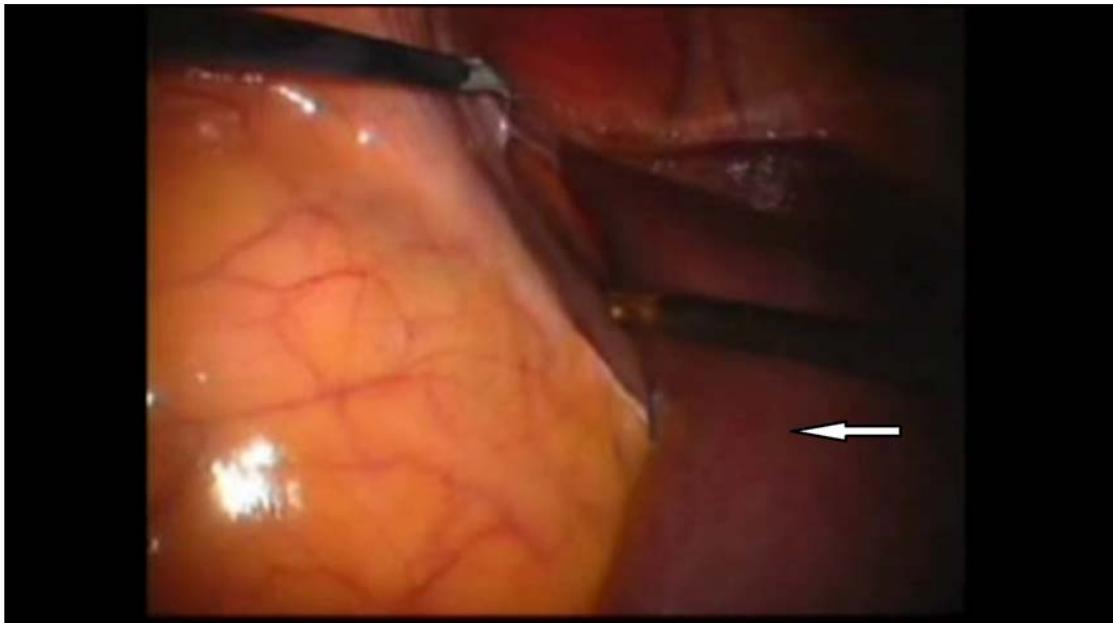
Figure 1.12 The lateral border of the inferior vena cava is dissected and the short main adrenal

vein is identified
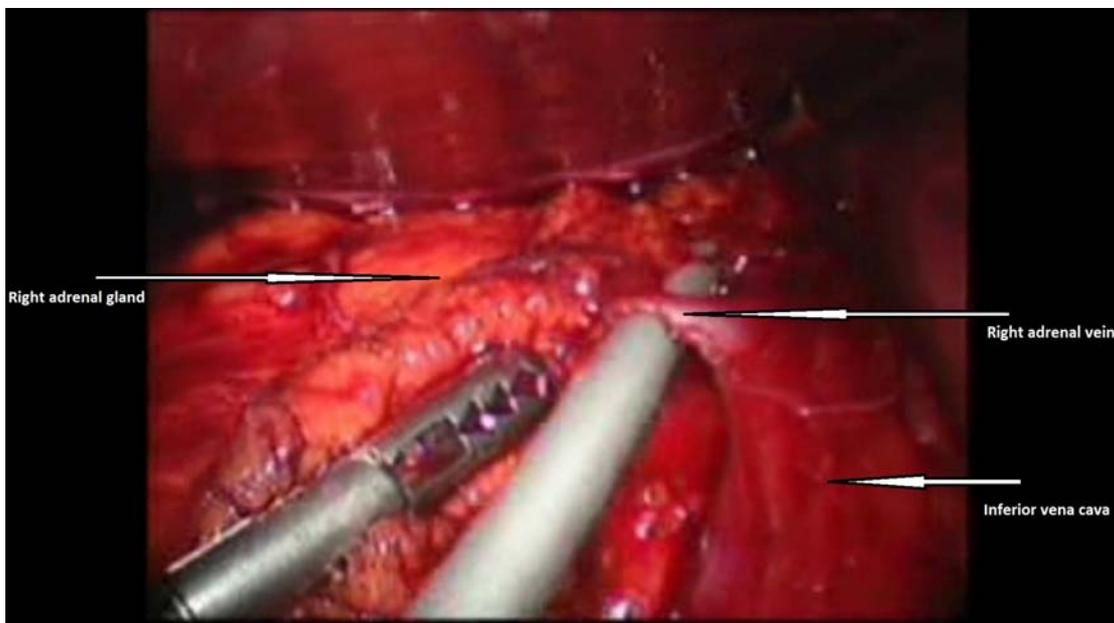
1.8.4 Technique modifications for larger adrenal tumours

The laparoscopic technique was modified for large adrenal tumours. On the right side, initial dissection of the inferior vena cava and the adrenal vein is often impossible due to tumour size. We like other authors (Henry, Sebag, Iacobone, & Mirallie, 2002) start dissecting laterally, superiorly and inferiorly (often alternating between these sites). This progressive mobilisation then allows access to the inferior vena cava and the procedure continues as described above. Similarly, on the left, initial adrenal vein dissection may not be possible due to tumour size. Primary lateral, superior, inferior dissection and mobilisation allows access to the adrenal vein. Often, it is not possible to insert these large tumours into a retrieval bag. In these cases a wound protector is inserted and the tumour is removed directly through the wound.

1.8.5 Uncertainty of laparoscopic adrenalectomy for large (≥6cm) potentially malignant tumours

It is uncertain if the resection of large (≥6cm) potentially malignant adrenal tumours is appropriate due to concern over incomplete resection and local recurrence. Although LA for large adrenal tumours has successfully been performed with good oncological outcomes the results need to be interpreted with caution. Reasons for this include: selection for those suitable for laparoscopy was practised in many published series and patient numbers tended to be small or follow-up was not adequate. Table 1.6 shows the outcome of studies for the laparoscopic removal of large adrenal tumours.

Table 1.6 Laparoscopic adrenalectomy for large adrenal tumours

Author	LA≥6cm over Total LA*	No of patients with malignancy°	Tumour size (cm)†	Conversion	Incomplete resection	Local recurrence	Mets	Follow-up† (months)
(Henry et al., 2002)	19/233 (8%)	6 (6)	7 (6-8)	2	0	0	1	35 (17-59)
(MacGillivray, Whalen, Malchoff, Oppenheim, & Shichman, 2002)	12/60 (20%)	3 (1)	8 (6-12)	0	0	0	1	24.5 (4-42)
(Walz et al., 2005)	33/429 (8%)	6 (2)	7.3 (2.1)¶	2	n.a.	2	5	n.a.
(Palazzo et al., 2006)	19/391 (5%)	3(3)	6.5 (6-8)	0	n.a.	1	2	25 (13-46)
(Soon et al., 2008)	16/140 (11%)	3 (3)	n.a.	4	n.a.	0	1	18 (n.a.)
(Ramacciato et al., 2008)	20/107 (19%)	4 (2)	8 (7-9)	3	0	0	1	n.a.

* Values in parentheses are percentage of LA for tumours ≥6cm or ≥7cm in the case series
    Tumours are 7cm or larger
° Values in parentheses are numbers of primary adrenal cortical carcinomas
† Values are median (IQR)
¶ Value is mean (sd)
n.a. , data not available

1.8.6 Laparoscopic subtotal adrenalectomy

Laparoscopic subtotal adrenalectomy has emerged as a feasible option allowing either bilateral adrenal medulla resection or partial adrenal cortex resection in patients with a single remaining adrenal gland (Hardy & Lennard, 2008). Case series have reported the procedure is most strongly indicated in patients with bilateral phaeochromocytoma (familial) or patients with aldosterone or cortisol producing tumours who have had previous contralateral adrenalectomy. This has been shown to preserve endogenous steroid production and allow independence from oral steroid therapy in the majority of patients (Brauckhoff et al., 2003).

Selection for subtotal adrenalectomy has generally been performed in small, well circumscribed, peripherally located lesions. Concern exists if the main adrenal vein is divided this may result in a non-functioning adrenal remnant.

It remains unclear from the literature, the true incidence of this procedure compare as totality of adrenalectomy practice is rarely reported. Results from small studies have reported no incomplete resections or local recurrences (follow-up range:3 months – 3 years) (Walz et al., 1998)(Kok & Yapp, 2002).

1.8.7 Open adrenalectomy

LA has become the procedure of choice for most adrenal pathologies but few have documented the incidence or outcomes of open adrenalectomy within a laparoscopic series. Therefore the results of open adrenalectomy in the laparoscopic era are unclear.

The open approaches to the adrenal gland include: posterior (extraperitoneal), flank (extraperitoneal), transabominal or thoracoabdominal.

For the posterior approach the patient is placed in the prone jackknife position. A hockey stick incision is made over the twelfth rib. The eleventh and twelfth ribs are often resected extrapleurally to allow access. The perinephric fat is swept away from the paraspinal musculature and the adrenal tumour is resected in an extraperitoneal manner. On the right the liver (within the peritoneum) is dissected off the anterior surface of the adrenal. A chest drain may be required if the pleura is breached. Disadvantages include restricted access. This technique is only suitable for small lesions.

An alternative extraperitoneal technique is the flank approach. The patient is placed in the lateral position (adrenal pathology uppermost) and the table is broken to allow increased space between the costal margin and iliac crest. An incision is made over the 11th or 12th rib and the relevant rib is resected. The dissection continues as for the posterior approach. Advantages include improved access compared to the posterior approach. Disadvantages include inability to perform abdominal exploration or adjacent structure resection in the presence of local invasion (other than kidney).

The transabdominal approach is by a midline or subcostal incision. The right adrenal is approached after Kocher's mobilization of the duodenum. On the left access is gained by dividing the lienorenal ligament and Toldt's fascia and sweeping the viscera forward. The advantages of this approach include resection of adjacent organs in the presence of local

invasion and bilateral adrenalectomy can be performed without changing patient position or utilising a separate incision.

The thoracoabdominal approach provides the best access for very large adrenal tumours or where wide resection of adjacent organs is anticipated. The thoracoabdominal 9th or 10th rib approach is used.

In the present series, the only contraindications to the laparoscopic approach were radiological locally advanced adrenal tumours requiring en-bloc resection of adjacent organs or the requirement of an additional open procedure. Therefore, in our series, the transabdominal or thoracoabdominal approach was felt to be the open technique of choice.

2 Summary and aims for the present work

2.1 Summary

1. The adrenal gland vasculature has been studied in a number of cadaver studies. However, the studies were carried out on non-diseased adrenal glands. It is not known if adrenal tumours, because of angiogenesis or vasodilatation of pre-existing vessels, may increase the variability of venous drainage and the number of periadrenal vessels.

2. After subtotal adrenalectomy, a satisfactory blood supply to the adrenal remnant is vital to preserve function. It is not clear from the literature whether a preserved main adrenal vein is essential for remnant function. Nor is it clear, at time of surgery, that excessive mobilisation would destroy the arteries surrounding the adrenal gland and lead to an ischaemic, non-functioning adrenal remnant.

3. Few studies have compared the perioperative haemodynamic variables for laparoscopic adrenalectomy for phaeochromocytoma resection and other adrenal tumours.

4. The role of laparoscopic adrenalectomy for large adrenal tumours (≥6cm) is controversial due to concerns over incomplete resection and local recurrence. As a result many surgeons opt for an open approach.

5. There is currently little information on the results of open adrenalectomy in the laparoscopic era as totality of adrenalectomy practice is rarely reported.

6. Due to the rarity of isolated adrenal metastasis, little is known about the role of laparoscopic adrenalectomy in this highly select group of patients.

2.2 Aims of thesis

The aims of the present work are:

1. To document the surgical importance of variable vein anatomy and multiple periadrenal vessels during the excellent magnified view experienced with laparoscopic adrenalectomy.

2. To review the importance of the adrenal gland blood supply when performing a laparoscopic subtotal adrenalectomy.

3. To look at the perioperative haemodynamic changes in patients undergoing laparoscopic adrenalectomy for phaeochromocytomas and other adrenal tumours.

4. To assess the role of laparoscopic adrenalectomy for adrenal tumours of 6cm or greater.

5. To assess the outcomes of open adrenalectomy in a consecutive series of patients referred with adrenal tumours.

6. To assess the role of laparoscopic adrenalectomy for isolated adrenal metastasis.

2.3 Database

The data of consecutive patients referred for adrenalectomy were extracted from a computerised database from January 1999 – January 2009. This data included patient name, date of birth, unit number and tumour characteristics (which included abnormal main venous drainage). All adrenalectomies were performed by a single surgeon (PJOD). The database was maintained by PJOD.

Case notes were then reviewed to extract additional patient data which included: patient physiology and follow-up.

3 Experience in identifying the venous drainage of the adrenal gland during laparoscopic adrenalectomy

3.1 Introduction

The venous drainage from each adrenal gland, described in standard anatomical textbooks, is usually via a single vein: the right one to join the inferior vena cava (IVC) and the left one to join the left renal vein (Gray & Williams, 1989). Variations to this pattern have been documented in a number of cadaver studies (Table 3.1).

Table 3.1 Variability of main venous adrenal drainage

Author (year)	Number of cadavers	Standard venous drainage Right side	Variable venous drainage Right side	Standard venous drainage Left side	Variable venous drainage Left side
(Anson & Caudwell, 1948)	450	450	0	449	1
(Johnstone, 1957)	10	8	2	9	1
(Clark, 1959)	16	9	7	11	5
(Mikaelsson, 1970)	22	22	0	22	0
(El-Sherief, 1982)	20	14	6	20	0
(Monkhouse & Khalique, 1986)	57	27	18	57	0

* 12 right adrenal glands not suitable for dissection

(Anson & Caudwell, 1948), in a study of 450 cadavers, confirmed the constant venous drainage. It was not clear from this study of kidney and adrenal gland blood supply, if the main adrenal vein was dissected in all cadavers or if a more selective policy was used. However, results of subsequent cadaver studies which focused on the venous drainage in normal adrenal glands described increased variability of the main venous drainage (particularly on the right side) and a network of veins surrounding the adrenal gland (Johnstone, 1957)(El-Sherief, 1982)(Monkhouse & Khalique, 1986). The variability in terms of duplication, triplication and termination of the main adrenal veins were described in these studies. The arterial supply of

the adrenal glands has been well documented. (Anson & Caudwell, 1948), described the arterial supply of the adrenal glands, in that they can receive up to 60 rami (small arteries) derived from aorta, inferior phrenic and renal arteries.

Since it was first introduced in 1992 (Gagner et al., 1992), laparoscopic adrenalectomy (LA) has become the procedure of choice for most adrenal pathologies. During LA, early identification and ligation of the main adrenal vein is an important step (Gagner, Pomp, Heniford, Pharand, & Lacroix, 1997). This is mainly to help orientation and prevent excessive haemorrhage.

The cadaver studies mentioned above were performed on non-diseased adrenal glands. It is not known if adrenal tumours, due to angiogenesis or vasodilatation of pre-existing vessels, may increase both the variability of venous drainage and the number of periadrenal vessels.

The purpose of this study was to document the importance of variable adrenal vein anatomy and the multiple periadrenal vessels during LA.

3.2 Methods

A retrospective review of our own consecutive laparoscopic adrenalectomy series was performed (January 1999 – January 2009). Details of the main adrenal veins and any periadrenal vessel variant had been recorded in each operation note. During laparoscopy, the main adrenal veins were identified and then divided between liga-clips. Other periadrenal vessels were divided using electrocautery or ultrasonic dissection (use of ultrasound to cut or coagulate vessels).

Preoperative information included: patient demographics and diagnosis. Intraoperative information included: details on the main venous drainage, any variant arterial or venous anatomy and any bleeding complications. Postoperative data included any further bleeding complications and the requirement for intervention.

3.3 Results

Over the ten year period, 176 laparoscopic adrenalectomies (LA) were performed on 156 consecutive patients (17 bilateral procedures, 3 patients delayed contralateral procedure).

Of the 176 LA, the main adrenal vein was identified in all cases at time of laparoscopy. For 170 LA, the main venous drainage was constant via a single vein (the right adrenal vein into the IVC and the left adrenal vein into left renal vein).

For the other six patients, the main venous drainage was variable. Characteristics of the patients with a variable venous pattern are shown in Table 3.2.

Table 3.2 Characteristics of patients with variable venous drainage

Patients	Side	Pathology	Size (mm)	Type of variability	Blood loss (mls)	Type of bleeding problems
1	Right	Phaeo	80	2 adrenal veins into IVC	200	Large tumour ooze from periadrenal vessels
2	Left	Phaeo	30	1 adrenal vein into left renal vein 1 adrenal vein unclear site of drainage	Minimal	None
3	Left	Phaeo	80	2 adrenal veins into left renal vein	Minimal	None
4	Left	Phaeo	55	2 adrenal veins into left renal vein	Minimal	None
5	Right	ACC	150	1 adrenal vein into IVC 1 adrenal vein into right renal vein	Minimal	None
6	Left	Phaeo	70	2 adrenal veins into left renal vein	Minimal	None

ACC = adrenocortical carcinoma, Phaeo = phaeochromocytoma

In each case the main adrenal vein was duplicated. In 5 out of the 6 patients the two veins were clearly visualised draining into the left renal vein, right renal vein or inferior vena cava at separate points. For the other patient with a left sided phaeochromocytoma, the drainage of the second adrenal vein was unclear. There were no bleeding complications due to failure to identify or ligate the adrenal vein variants. Of the six patients, only one had measurable blood

loss (200mls). This patient had a large (8cm) phaeochromocytoma with persistent ooze from the multiple periadrenal vessels. Conversion to an open procedure was performed due to concern over adjacent structure invasion. There were no other converted procedures for patients with variable adrenal vein drainage. The patient with a right adrenocortical carcinoma had a prominent, dilated second adrenal vein draining into the right renal vein. This has been illustrated by a magnetic resonance image (MRI) (Figure 1).

Figure 3.1 Magnetic resonance image to illustrate duplicate adrenal vein for a patient with a large adrenal tumour

MRI adrenal to illustrate duplicate adrenal vein for a patient with a large adrenal tumour
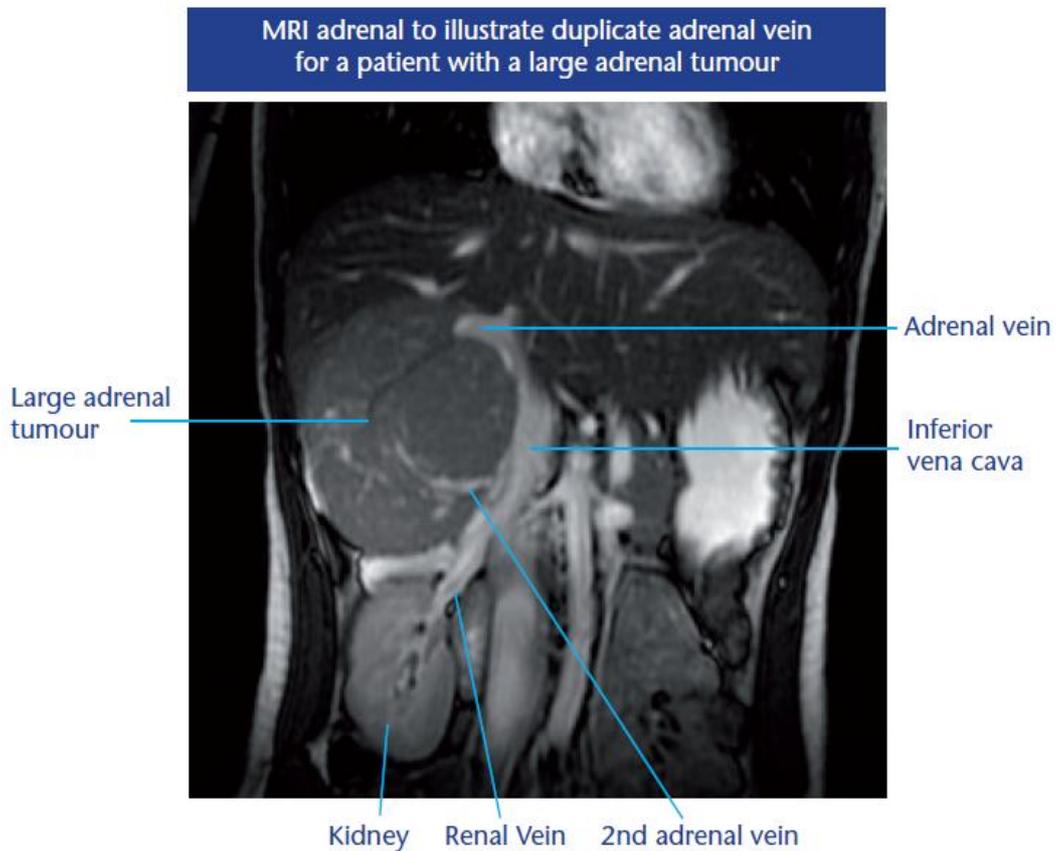
The characteristics of phaeochromocytomas with variable venous drainage compared to those with standard venous drainage are shown in Table 3.3.

Table 3.3 Characteristics of patients with phaeochromocytomas

Characteristic	Variable venous drainage	Standard venous drainage
Type of secretion		
Epinephrine	2	6
Norepinephrine	1	7
Dopamine	0	1
Epinephrine/Norepinephrine	0	8
Epinephrine/Norepinephrine/Dopamine	0	5
Catecholamine metabolites*	2	6
No secretion	0	1
Size (maximum diameter, mm)†	66 (33-75)	50 (34-59)

* Defined as elevation of urinary methoxy-derivatives or vanillyl mandelic acid
† Median (interquartile range)

Both groups secreted a range of catecholamines. The median size of the phaeocromocytomas with adrenal vein variants was 66mm (IQR33-75) compared to a median of 50mm (IQR34-59) for those with standard venous drainage.

During laparoscopy, apart from the main adrenal vein, a high number of other small vessels were always present around the adrenal gland. It was not possible to differentiate between veins and arteries. These were all dealt with in the same way, by diathermy or ultrasonic dissection. Due to the small size of these vessels there was no requirement to perform other haemostatic techniques. No laparoscopic procedure required conversion due to bleeding from these smaller vessels. For four patients with large (≥6cm) phaeochromocytomas (n=3) and an adrenal metastatic deposit secondary to renal cell carcinoma (n=1) there were increased number of periadrenal vessels. These were all divided without incident by careful ultrasonic dissection. The main venous drainage was by a single vein for these patients. In one patient with a phaeochromocytoma, the patient initially looked to have a duplicated left adrenal vein. As dissection progressed the second vein was found to travel into perinephric fat without obvious communication with the phaeochromocytoma.

3.4 Discussion

The majority of patients (97%) undergoing LA had constant venous drainage. This was via a single vein draining into the inferior vena cava on the right and draining into left renal vein on the left. When variation did occur, the main vein was duplicated. Other multiple, small periadrenal vessels were noted at time of laparoscopy for all patients. It was not possible to distinguish between small veins and arteries. The small periadrenal veins which do exist may provide alternative venous drainage pathways. However, in the current study, they did not cause any surgical significance as they were all divided easily using electrocautery or ultrasonic dissection.

Laparoscopy allows an excellent, magnified view (2.5-3 times normal) of the adrenal gland and surrounding structures compared to the traditional view seen at open surgery. Despite these advantages, it is not known if laparoscopy allows an accurate view of the venous anatomy. Identification of the main adrenal vein is an essential part of LA (Gagner et al., 1997). This study has demonstrated the main venous drainage (including variants) can be clearly defined at time of LA for all cases. No bleeding complications or the requirement to convert to an open procedure resulted from failure to recognise the main adrenal vein and its variants.

A number of series have dissected adrenal veins in cadavers (Anson & Caudwell, 1948)(Johnstone, 1957)(Clark, 1959)(El-Sherief, 1982)(Monkhouse & Khalique, 1986). In all these series there was no adrenal gland pathology. In a large series of 450 cadavers, Anson et al. looked at the pararenal system of veins and arteries and commented on the constant nature of the venous drainage of the adrenal gland via a single vein. Only one variation occurred, where the left adrenal vein joined the right renal vein. There was no mention of duplication or triplication of the adrenal vein. However, it is not clear if the authors performed selected adrenal

vein dissection as the study did not specifically examine the venous drainage of the adrenal gland. There was also no mention of the network of smaller veins surrounding the adrenal gland. Therefore, this description of adrenal gland venous drainage should be interpreted with caution.

Subsequent series focused on venous drainage and highlighted the variable nature, particularly on the right side (Table 1). However, compared to Anson et al. (1948), the numbers in these series were much smaller (Johnstone, 1957; Clark, 1959; El-Sherief, 1982; Monkhouse et al.,1986). In these series, using fresh or embalmed cadaver material, variability on the right side was fairly constant, occurring in 20-40% of cases. The variability involved duplication or triplication of the main vein. Also alternative venous drainage occurred into the hepatic or renal veins rather than the inferior vena cava. Johnstone (1957), described for 2 out of 10 cadaver dissections, the right adrenal vein draining directly into a right hepatic vein close to its junction with the inferior vena cava.   Variability on the left side appeared to be infrequent in the majority of series. Clark (1959) and Johnstone (1957) commented on a duplicated left adrenal vein. Clark (1959) described 5 out of the 16 cadavers having duplication of the main vein with both draining into the left renal vein and Johnstone (1957), one out of 10 dissections had a second main vein draining into a left lumbar vein.

In the current series a variable main adrenal vein was infrequent. The single main left adrenal vein is in agreement with the majority of other studies. However, when variation did occur, this was by a duplicated adrenal vein. This has been previously described by Clark (1959) and Johnstone (1957). The infrequent variability of the main right adrenal vein was in contrast to previous studies which focused on adrenal venous drainage. When variation did occur this was as a duplicated vein as previously described by Johnstone, 1957; Clark, 1959; El-Sherief, 1982; Monkhouse et al.,1986.

The presence of multiple periadrenal vessels has been well described in a number of anatomical studies. Johnstone (1957), in a series of 10 cadaver dissections, described multiple venules surrounding the adrenal gland and their drainage pattern. The venules could drain into the main adrenal vein, the perirenal fat veins, renal vein, inferior phrenic vein or lumbar vein. Anson et al. (1948) described the abundant arterial supply of the adrenal glands. They demonstrated up to 60 branches derived from the inferior phrenic, aorta or renal arteries can supply the adrenal gland. Folkman (1995), described the necessity of angiogenesis to allow tumour growth and then metastasize. Therefore, in the presence of an adrenal tumour, new periadrenal vessels could sprout from pre-existing vessels, which may lead to troublesome bleeding at time of laparoscopic adrenalectomy. These changes should become more apparent as the tumour increases in size. Our study, demonstrated the abundance of vessels around the adrenal gland. The periadrenal vessels did not represent a problem in the majority of cases. The vessels were controlled with electrocautery or ultrasonic dissection. However, for three patients with large phaeochromocytomas (≥6cm) and one patient with an adrenal metastasis there were an increased number of periadrenal vessels. Another patient with a large adrenocortical carcinoma (15cm) had multiple prominent vessels, particularly a tortuous, dilated second adrenal vein draining into the right renal vein. It is unlikely the second adrenal vein developed due to tumour angiogenesis. A possible explanation could be compression of the main adrenal vein (due to the mass effect of the tumour) which caused preferred venous return down the second adrenal vein.

In the current study the adrenal vein variants all occurred in patients with phaeochromocytomas or a large (15cm) adrenocortical carcinoma. Out of 39 patients with phaeochromocytomas, only 5 showed variant venous anatomy. The range of catecholamine secretion was comparable to phaeochromocytomas with standard venous anatomy. This is the first study to describe main adrenal vein variants during LA for a series of patients with

phaeochromocytomas. Other series have described only standard venous anatomy during LA for phaeochromocytoma (Cheah, Clark, Horn, Siperstein, & Duh, 2002)(Gotoh, Ono, Hattori, Kinukawa, & Ohshima, 2002).

Our study has demonstrated laparoscopic adrenalectomy can visualise the main venous drainage (and any variants) from the adrenal gland with minimal bleeding complications. This has helped confirm the constant nature of the main adrenal veins in the majority of patients undergoing laparoscopic adrenalectomy. However, adrenal vein variants and an increased number of periadrenal vessels appeared to occur in patients with phaeochromocytomas or large adrenocortical carcinomas. Increased care regarding the adrenal gland vasculature may be required during laparoscopic adrenalectomy for these patients.

4. Importance of the adrenal gland blood supply during laparoscopic subtotal adenalectomy

4.1 Introduction

Subtotal adrenalectomy was first described in 1934. Subtotal adrenalectomy allows either bilateral adrenal medulla resection or partial adrenal cortex resection in patients with a single remaining adrenal gland. The procedure has been performed in patients with a familial predisposition to phaeochromocytoma and patients with a cortisol or aldosterone producing adenoma who have had a previous contralateral adrenalectomy (Hardy & Lennard, 2008). Subtotal adrenalectomy has been shown to preserve endogenous steroid production and allow independence from oral steroid therapy in the majority of patients (Brauckhoff et al., 2003). The popularity of the procedure has been variable with only small series reported in the literature. Recently, improved preoperative imaging, excellent magnified views at time of laparoscopy and the use of ultrasonic dissection has resulted in increased number of patients to be considered for the procedure. It remains unclear from the literature the frequency of this procedure compared to the overall number of adrenalectomies performed as totality of practice is rarely reported.

After subtotal adrenalectomy, a satisfactory blood supply to the adrenal remnant is vital to preserve function (Ikeda et al., 2001). It is not clear from the literature whether a preserved main adrenal vein is essential for remnant function. Nor is it clear, at time of surgery, that excessive mobilisation would destroy the arteries surrounding the adrenal gland and lead to an ischaemic, non-functioning adrenal remnant.

The aim of the current study was to review the importance of the adrenal gland blood supply when performing a laparoscopic subtotal adrenalectomy.

4.2 Methods

The blood supply of the adrenal gland was examined in three ways.

An overview of the adrenal blood supply was studied in cadaver dissections. This involved a computer-assisted search of Medline database. The combinations and terms included: adrenal/suprarenal blood supply, adrenal/suprarenal arteries, adrenal/suprarenal veins and adrenal vein variants. The results have been summarised in Chapter 3 (Table 3.1).

A review of our own consecutive laparoscopic adrenalectomy series was performed (January 1999 – January 2009). The details of the main adrenal veins and variants had been recorded in each operation note. The results have been summarised in Chapter 3.

Cadaver dissection of adrenal glands was performed. The dissected cadavers were from Glasgow University Anatomy department. The arterial and venous supply was examined. The adrenal arteries were initially injected with latex/India ink mixture via the carotid artery. The adrenal gland and its surrounding tissue were cleared using the Spaltehoz technique (a 14 day technique using alcohol and then methyl salicylate in the final step). Photography was performed using a Wolfvision LB9 visualiser (WolfVision). The venous supply was examined using standard dissection and then histological techniques. A modified Masson's trichrome stain was used for microscopy.

4.3 Results

Literature overview

The main venous drainage described in cadaver studies has given differing results (Table 3.1). On the left side the adrenal gland appeared to be drained by a single main vein in the majority of the studies. Only Clark, 1959, in his study of 16 non injected cadavers, found duplication of the main left adrenal vein in 5 cases. On the right side, much more variation of the main adrenal vein was found. The main variants were duplication or triplication of the main adrenal vein.

Johnstone, Mikaelsson, El-Sherief and Monkhouse described the presence of smaller veins surrounding the adrenal gland (particularly on the lateral aspect). The nomenclature of these smaller veins varied: peripheral, capsular or superficial. Using venous contrast, Mikaelsson, 1970, described how these peripheral veins originated from the adrenal gland rather than the surrounding capsule or perirenal fat.

Arterial blood supply was found to be remarkably consistent between the cadaver studies. The arteries supplying the adrenal gland took their origin from the following sources: inferior phrenic artery, aorta and renal artery. All authors described multiple small arteries surrounding and entering the gland. Anson et al. (1948), describe 50-60 small arteries supplying the adrenal gland.

Adrenal vein variants visualised at time of laparoscopic adrenalectomy

Over the ten year period, details of the main adrenal vein and any variants have been documented in the results section of Chapter 3. During laparoscopy, apart from the main adrenal vein, a high number of other small vessels were always present around the adrenal gland. It was not possible to differentiate between veins and arteries.

Cadaver dissection

Arterial supply

4 adrenal glands with intra-arterial latex were cleared of periadrenal fat using techniques described in the methods section. There were 2 left sided and 2 right sided glands. The arteries originated from the inferior phrenic artery, the aorta and the renal artery. Division occurred in the fat surrounding the adrenal gland. The large number of small arteries surrounding and entering the adrenal glands are demonstrated in Figure 4.1.

Figure 4.1 The images show semi-cleared adrenal glands. **A** is a left adrenal gland. **B** shows a right adrenal gland. Arterial vessels are seen in black due to latex/Indian ink injection

Superior Adrenal Artery
(Inferior Phrenic Artery)

Middle Adrenal Artery
(Aorta)

Left
Kidney

Inferior Adrenal Artery
(Renal Artery)

Renal Artery

Lt Adrenal Vein

A

Lt Renal Vein

Superior Adrenal Artery
(Inferior Phrenic Artery)

Middle Adrenal Artery
(Aorta)

Inferior
Adrenal
Artery
(Renal
Artery)

B
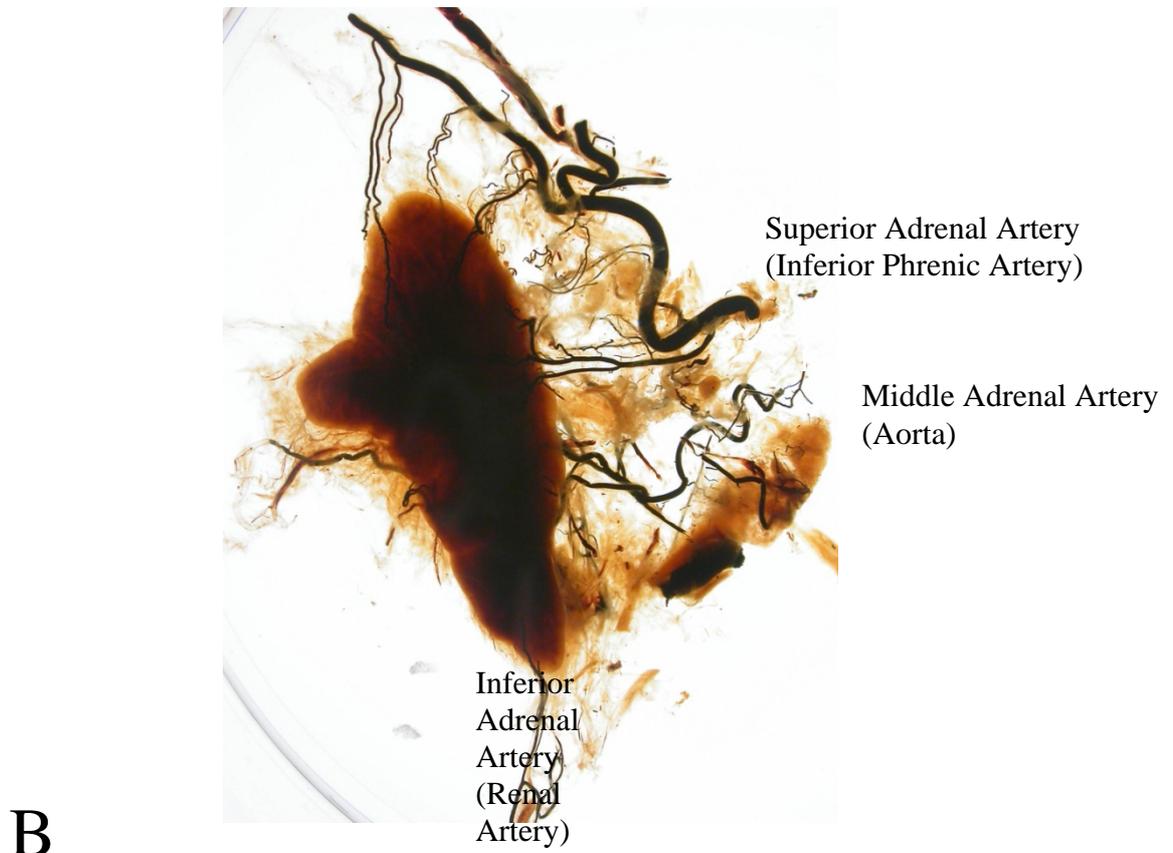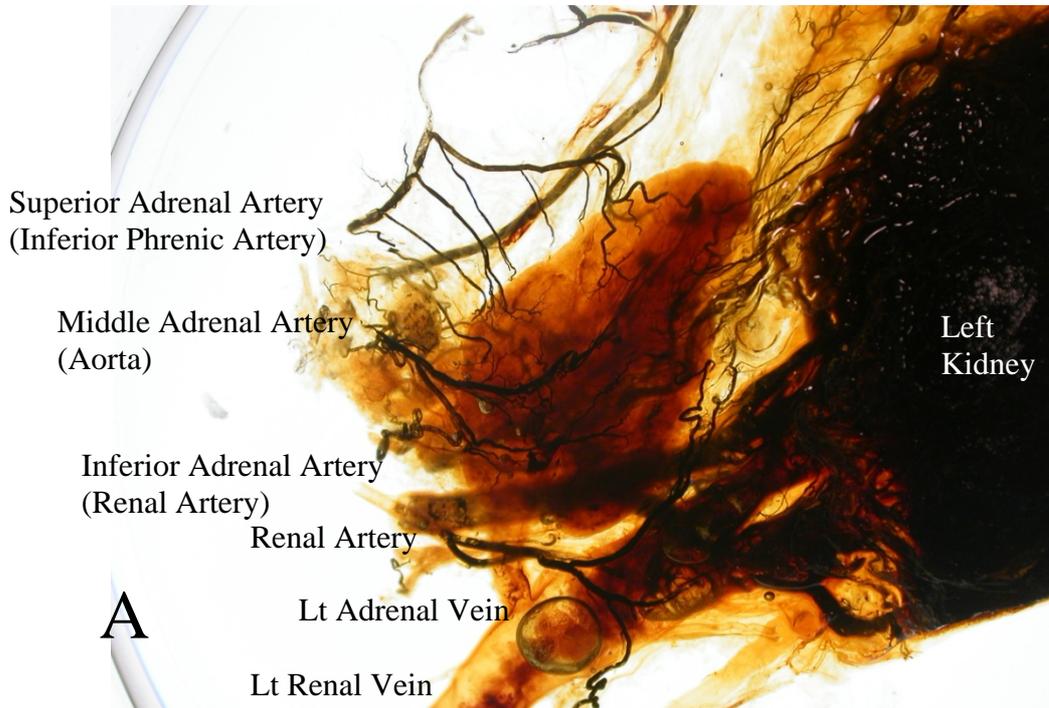
Venous drainage

The venous drainage was studied in 4 adrenal glands (2 left and 2 right). Using standard dissection techniques, the main venous drainage was via a single vein: the right one to join the inferior vena cava and the left one to join the left renal vein. However, a large number of smaller peripheral veins follow the numerous arteries surrounding the adrenal gland. These vessels leaving the lateral aspect of a left adrenal gland are demonstrated in Figure 4.2.

Figure 4.2 Dissection of lateral surface of the adrenal gland
AG, left Adrenal Gland. Peripheral veins (veins are white, arteries are black)
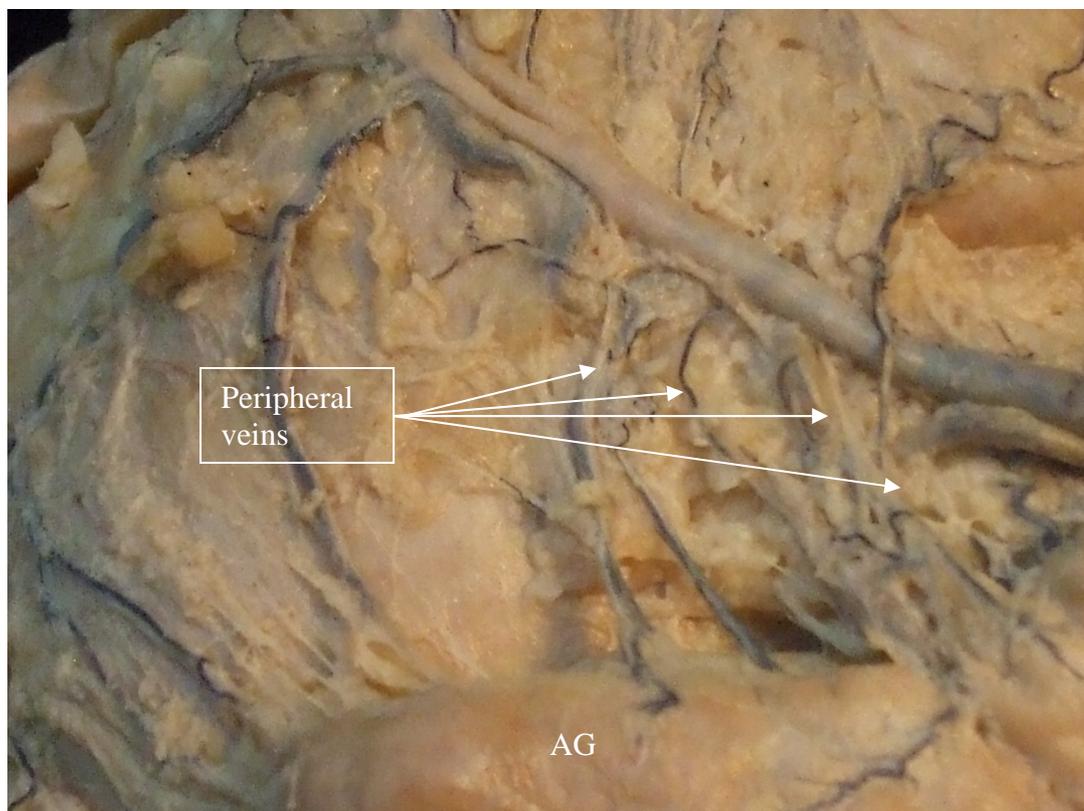
These lateral placed veins were studied on histological slides to ensure they were actually draining the gland rather than running along the surface. Microscopic examination was performed in 2 cases (one left and one right). This confirmed the veins drained the lateral aspect of the gland. Figure 4.3 demonstrates a peripheral situated vein progressively leaving the gland on repeated sectioning.

Figure 4.3– Five sections (I-V) showing a central vein (c) in the medulla (I) which is drained by a superficial vein (v) penetrating the capsule (IV), into the perinephric fat (V).

(I)

(II)

(III)

(IV)

(V)
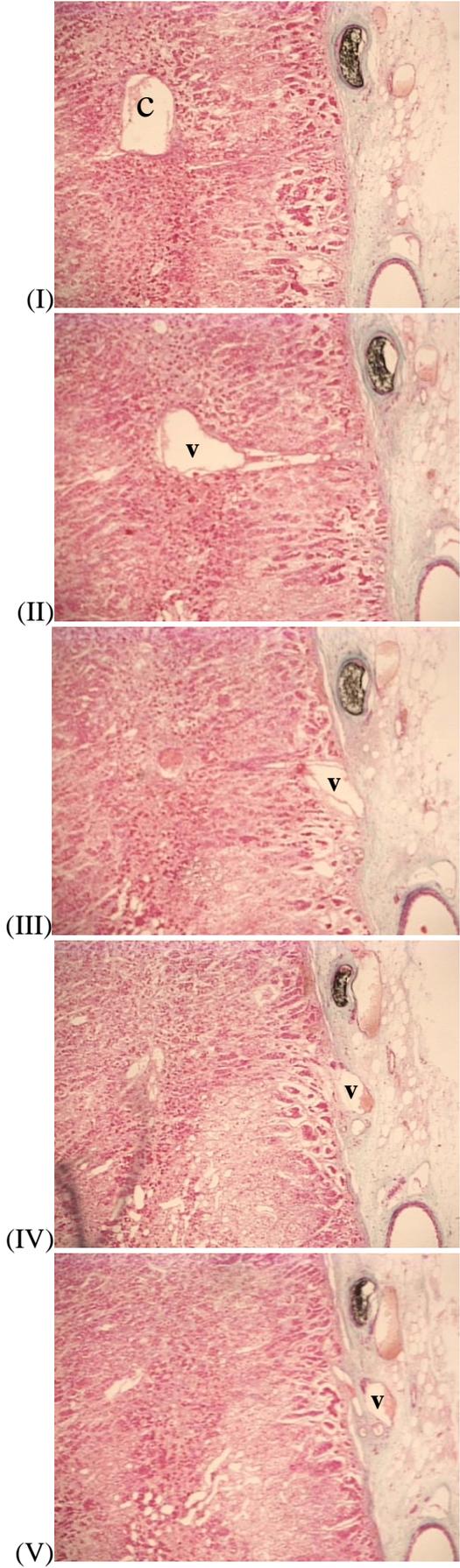
4.4 Discussion

Laparoscopic subtotal adrenalectomy is becoming an attractive option in certain patients with adrenal pathologies (eg familial phaeochromocytomas, aldosterone producing adenomas, cortisol producing adenomas). This can eliminate the need for hormone substitution in the majority of patients. Adequate arterial supply and venous return is essential to allow a resulting functioning adrenal remnant for patients undergoing subtotal adrenalectomy.

This study has shown from our own and previous cadaver dissection multiple small arteries completely surround the adrenal gland. The main adrenal vein was remarkably constant. However, when variation does occur this was usually duplicated or triplicated. In addition to the main adrenal vein, cadaver studies have shown a network of peripheral veins surround the adrenal gland. These veins were closely related to the arteries.

From the small series describing subtotal adrenalectomy it was not clear whether preservation of the main adrenal vein was essential to allow subsequent adrenal remnant function. Imai et al described laparoscopic subtotal adrenalectomy in 5 patients (aldosterone producing adenoma or weak functioning adrenocortical adenoma) with preservation of the main adrenal vein (Imai et al., 1999). The authors' hypothesised preservation of the main vein was essential to avoid venous congestion which would lead to a non-functioning remnant. The resultant function of the adrenal remnant was not reported. Roukounakis et al, reported the importance of adrenal vein preservation for 7 patients undergoing subtotal adrenalectomy for aldosterone producing adenomas or myelolipomas. Again, details of post-operative adrenal function was not reported (Roukounakis et al., 2007). (Janetschek et al., 1998), described subtotal adrenalectomy in 6 patients with inherited phaeochromocytoma. In a mean follow-up of 18 months there were no recurrences. The authors felt preservation of the main vein was essential to allow for a functioning adrenal remnant.

Ikeda et al felt the adrenal vein could be divided without consequence to the adrenal remnant (Ikeda et al., 2001). They described subtotal adrenalectomy with main vein division for 6 patients (aldosterone producing adenoma, inherited phaeochromocytoma). Postoperative adrenal function was assessed by I-adosterol scintigrams. However, scintigraphy is not a suitable test to determine sufficient endocrine function. Brauckhoff et al, advocated a selective approach to division of the main adrenal vein depending on the site of the adrenal tumour (Brauckhoff et al., 2003). Of the 14 patients, 4 patients underwent bilateral subtotal adrenalectomy with division of the main adrenal vein. No patient required substitution with exogenous steroids. Postoperative adrenal function was assessed by serum levels of cortisol and adrenocorticotropic hormone (ACTH) within the normal range. Walz and colleagues demonstrated similar findings (Walz et al., 1998). Subtotal adrenalectomy was performed in 2 patients with bilateral hereditary phaeochromocytoma. Postoperative cortisol levels were within the normal range.

In Chapter 3 our laparoscopic study has shown the consistency of the main adrenal vein. 170 out of 176 laparoscopic arenalectomies the main adrenal vein was single and originated from the same site. Duplication of the main adrenal vein occurred in 6 cases. A number of peripheral vessels always surrounded the gland. It was not clear at laparoscopy if these represented arteries or veins. Overview of cadaver studies assessing the venous drainage of the adrenal gland consistently demonstrated smaller veins surrounding the adrenal gland. Mikaelsson examined adrenal venous drainage in 22 fresh cadaver specimens (Mikaelsson, 1970). The cadavers had been injected with contrast into the vena cava. Using a combination of dissection and radiological examination the author demonstrated these peripheral veins drained the adrenal gland.

We have demonstrated using gross dissection and histological methods it was possible to follow the venous drainage from the adrenal gland to these peripheral veins. This has helped establish the peripheral veins drain the adrenal gland.

Therefore, we support the findings of Brauckhoff and Walz, that division of the adrenal vein can be performed safely without causing venous congestion and non-functioning of the adrenal remnant. However, when the main adrenal vein is divided excessive mobilisation of the adrenal gland should be avoided due to concern the above mentioned peripheral veins may be destroyed and potentially result in a non-functioning adrenal remnant.

It was clear from our cadaver dissection the adrenal gland is supplied by many small arteries which surround the gland. This is in agreement with (Anson & Caudwell, 1948). In their study of 450 cadavers it was observed the adrenal gland is supplied by up to 60 small arteries originating from the aorta, inferior phrenic and renal arteries. Therefore, it would appear unlikely the adrenal remnant would become ischaemic due to inadequate arterial supply during subtotal adrenalectomy. Almost complete mobilisation of the adrenal remnant would be required to achieve this.

Factors other than adrenal blood supply should also be considered to preserve adrenal remnant function. Selection is important as small, isolated, peripheral and well demarcated lesions are most suitable. Centrally placed lesions can make the procedure more demanding or in some cases impossible. At initial dissection a decision is made to divide or preserve the adrenal vein. Careful mobilisation of the adrenal tissue containing the lesion is performed. Subtotal adrenalectomy is then performed using ultrasonic dissection. Using this technique, collateral damage to adjacent tissue is limited to less than 5mm. Alternatively, a vascular stapler can be utilised. However, it is important to leave sufficient functioning adrenal remnant.

Brauckhoff and colleagues, in a series of 22 patients, recommended adrenal remnant size < 25% of normal gland size should be avoided to prevent adrenal hypofunction. The authors used intraoperative ultrasound to determine normal adrenal tissue and identify the resection margins.

Conclusion

This study has helped show, during laparoscopic subtotal adrenalectomy, a non functioning adrenal remnant is unlikely due to an inadequate arterial supply. Division of the main adrenal vein can be performed safely without risk of venous congestion. However, once the main adrenal vein is divided, extensive mobilisation of the adrenal remnant should be avoided to prevent destruction of the smaller peripheral veins necessary for venous drainage.

5. Perioperative haemodynamic changes in patients undergoing laparoscopic adrenalectomy for phaeochromocytomas and other adrenal tumours

5.1 Introduction

Laparoscopic adrenalectomy (LA) has become a well established operation for phaeochromocytoma resection and results in improved hospital stay and shorter convalescence when compared to open adrenalectomy (Gagner et al., 1997)(Assalia & Gagner, 2004)(Fernandez-Cruz, Taura, Saenz, Benarroch, & Sabater, 1996). However, both pneumoperitoneum and adrenal gland manipulation have been shown to cause a high level of catecholamine release during laparoscopic resection (Joris et al., 1999) (Tauzin-Fin et al., 2004). This can result in haemodynamic changes in the form of severe hypertension (systolic blood pressure (SBP) >200mmHg) and cardiac arrhythmias (Inabnet, Pitre, Bernard, & Chapuis, 2000)(Kinney et al., 2000). Subsequent removal of the adrenal gland results in a marked decrease in catecholamines and can induce hypotension which may be refractory to fluid or alpha agonist therapy (Prys-Roberts, 2000).

A number of studies have documented the perioperative haemodynamic changes during phaeochromocytoma resection using a variety of regimens to control arterial blood pressure. For example, Kinney et al, studied 143 patients who received preoperative phenoxybenzamine (a long acting non selective alpha blocker). Despite this, 20 patients (14%) experienced very severe intraoperative severe SBP>220mmHg. Other regimens such as calcium antagonists are an alternative to phenoxybenzamine. Lebuffe et al used preoperative oral nicardipine, 27 out of 105 patients (26%) experienced severe SBP>200mmHg, 12% experienced persistent hypotension and 30% experienced a tachycardia (heart rate>120bpm). However, in both of these studies only 3% and 22% (respectively) of patients underwent a laparoscopic procedure. In the current series, we used a phenoxybenzamine regimen and felt complete alpha blockade was achieved in all cases. As a result, we felt using this regimen and a specialist endocrine,

anaesthetic and surgical team the perioperative haemodynamic stability of LA for phaeochromocytoma has improved to such a degree that they may now be comparable to LA for other non-catecholamine secreting adrenal tumours.

A small number of studies have compared the laparoscopic perioperative haemodynamic changes of phaeochromocytoma resection with other adrenal tumours (Gotoh et al., 2002)(Weismann et al., 2006)(Kim, Brennan, Russo, Burt, & Coit, 1998a). Unfortunately, the numbers tended to be small or the laparoscopic technique was used infrequently.

Therefore, the aim of the present study was to compare the perioperative haemodynamic changes in consecutive patients undergoing LA for phaeochromocytomas and other adrenal tumours during the same period.

5.2 Methods

From January 1999 to January 2009, details of patients who underwent laparoscopic adrenalectomy were identified from a prospective database. Perioperative physiology parameters were obtained by performing a retrospective case note review.

The diagnosis of phaeochromocytoma was based on clinical, biochemical and imaging studies. Clinical presentation included intermittent episodes of palpitations, sweating, headaches and hypertension. Patients from an affected family or genetic syndromes (eg MEN2 or von Hippel-Lindau) were also screened. Biochemical screening included 24 hour urine collections for the measurement of fractionated catecholamines and their metabolites (metanephrines and vanillymandelic acid (VMA)). Localization of the tumour was by computed tomography (CT) or magnetic resonance imaging (MRI) scans. I-meta-iodo-benzylguanidine (MIBG) nuclear scanning was used to detect metastatic disease or extra-adrenal paraganglioma. These patients were called the phaeochromocytoma group.

The diagnosis of other adrenal tumours was based on clinical findings and hormonal assessment. Localization of the tumour was by CT or MRI. These patients were called the non-phaeochromocytoma group.

At initial endocrine assessment, all patients with a suspected phaeochromocytoma received oral phenoxybenzamine as the primary alpha blocker (range 10-60mg/day). This was titrated to achieve a blood pressure measurement <160/90 mmHg. Patients, who were hypertensive, were often taking other anti-hypertensive medication, usually initiated by the referring physician prior to the diagnosis of phaeochromocytoma. This included: beta-blockers, ACE inhibitors, calcium antagonists and loop and thiazide diuretics. Patients were not routinely beta-blocked in the preoperative period. Hypertension was controlled in all phaeochromocytoma patients prior to elective resection. Patients who were hypertensive in the non phaeochromocytoma group received a variety of anti-hypertensives, again dependant on the referring physician, including:

beta-blockers, ACE inhibitors, calcium antagonists and loop and thiazide diuretics. Once a diagnosis of Conn's syndrome was made, additional potassium-sparing diuretics were introduced (spironolactone or amiloride).

All patients in the phaeochromocytoma group received an infusion of phenoxybenzamine (1mg kg^{-1}, a non selective alpha blocker) the day before LA. Oral phenoxybenzamine was discontinued the day before theatre.

General anaesthesia was performed by a single anaesthetist. The following technique was used: induction was with a combination of fentanyl, propofol and a muscle relaxant, and maintenance by volatile agents (isoflurane, sevoflurane) in an air/oxygen mixture and morphine as a bolus or infusion. Arterial blood pressure was monitored either by a radial arterial line or by a non-invasive oscillometric blood pressure cuff (measured every three minutes). Pulse and blood pressure measurements were recorded on to an anaesthetic chart every five minutes. Laparoscopic adrenalectomy was performed using the lateral transabdominal approach. During surgery for phaeochromocytoma, episodes of hypertension (SBP>180mmHg) were treated with intravenous phentolamine (boluses 1 to 2mg) and/or labetalol (boluses 5 to 10mg). Tachycardia was treated with intravenous labetalol (boluses 5 to 10mg). Hypotension was treated with fluid boluses (crystalloid or colloid) and/or an intravenous vasopressor (metaraminol).

Preoperative information included age, sex, diagnosis, blood pressure measurement, antihypertensive medication and in the case of phaeochromocytomas the preoperative levels of urinary or plasma catecholamines. Intraoperative information included method of anaesthesia, total anaesthetic time, all pulse and blood pressure recordings, use of antihypertensives, use of intravenous fluids or blood products and operative complications. Postoperative information included recovery room haemodynamic measurements, the use of vasopressors and the requirement of intensive care admissions.

Severe hypertension was defined as SBP >200mmHg (Inabnet et al., 2000)(Gotoh et al., 2002)(Sprung et al., 2000) . A transient episode was defined as <10minutes and a persistent episode was defined as >10minutes.   Persistent tachycardia was defined as a heart rate >120bpm>10minutes (Lebuffe et al., 2005). Persistent hypotension was defined as SBP <80mmHg>10minutes (Lebuffe et al., 2005)(Kinney et al., 2000).

Statistical analysis

Categorical variables were compared using Chi-square and Fishers exact tests where appropriate. For continuous data median and interquartile range (IQR) or mean and range were calculated where appropriate. Analysis of continuous data was performed using the Mann-Whitney test. A p value of <0.050 was assumed to be statistically significant. Analyses were performed using SPSS (Version 17.0).

5.3 Results

Over the ten year period, 39 consecutive patients underwent 42 LA for phaeochromocytoma. Two patients underwent bilateral phaeochromocytoma resection for familial disorders (Von Hippel-Lindau and MEN 2B syndromes). Another patient underwent a delayed contralateral procedure for familial phaeochromocytoma. During the same period 117 consecutive patients underwent 134 LA for other adrenal tumours (non phaeochromocytoma). 15 patients underwent bilateral LA and 2 patients had a delayed contralateral procedure. Patient characteristics are listed in Table 5.1.

Table 5.1 Characteristics of 156 patients undergoing laparoscopic adrenalectomy

	Phaeochromocytoma group	Non phaeochromocytoma group
Number of patients	39	117
Sex ratio (M:F)	16:23	49:68
Age*	55 (29-84)	57 (18-79)
Preop heart rate (bpm)†	77 (70-90)	73 (63-82)
Preop SBP (mmHg)†	133 (117-152)	139 (129-156)

Preop=preoperative
SBP = Systolic Blood Pressure
*Values are mean (range)
ª3 patients had delayed contralateral adrenalectomy
† Values are median (interquartile range)

Preoperative data

The most commonly secreted catecholamines were epinephrine (n=8) and norepinephrine (n=8) (Table 5.2). One patient with a phaeochromocytoma was non-secreting on a background of multiple endocrine neoplasm (MEN) syndrome.

Table 5.2 Type of catecholamine secretion observed in 39 patients with phaeochromocytoma

Type of catecholamine secretion	Number of patients	Subgroups which experienced intraoperative SBP 200-220mmHg
Epinephrine	8	0
Norepinephrine[†]	8	1
Dopamine	1	0
Epinephrine/Norepinephrine	8	3
Epinephrine/Norepinephrine/Dopamine	5	3
Catecholamine metabolites*	8	0
Non secreting	1	0

SBP= systolic blood pressure
[†]One patient underwent delayed contralateral procedure (recurrent norepinephrine secretion)
* Defined as elevation of urinary methoxy-derivatives or vanillyl mandelic acid

All patients received oral phenoxybenzamine (range 10mg-60mg/day) at time of diagnosis. All patients with a phaeochromocytoma received an intravenous phenoxybenzamine infusion (1mg kg^{-1}) the day before surgery. The preoperative blood pressure was controlled in all patients prior to surgery (Table 5.1). In the phaeochromocytoma group, 37 out of 40 procedures had invasive measurement of arterial pressure compared to 14 out of 119 patients in the non phaeochromocytoma group.

Intraoperative data

Table 5.3 compares the intraoperative haemodynamic parameters between the two patient groups.

Table 5.3 Table to show intraoperative events between patients with phaeochromocytomas and non phaeochromocytomas

Intraoperative event	Phaeo (Number of procedures=40)	Non phaeo (Number of procedures=119)	P value
Transient severe hypertension (SBP>200mmHg <10 mins)	6	2	0.004
No transient severe hypertension	34	117	
Persistent severe hypertension (SBP>200mmHg >10 mins)	2	1	0.317
No persistent severe hypertension	38	118	
Antihypertensive treatment	22	2	<0.005
Persistent tachycardia (HR >120bpm >10mins)	2	1	0.317
No persistent tachycardia	38	118	
Persistent hypotension (SBP<80mmHg >10mins)	3	9	1.000
No persistent hypotension	37	110	
Fluid requirements (litres)†	1.5 (1-2.0)	1.5 (1-1.5)	0.114
Total anaesthetic time for unilateral LA (minutes)†	110 (85-150)	100 (80-130)	0.375

SBP=systolic blood pressure
HR=heart rate
† Values are median (interquartile range)

Seven patients experienced severe hypertension (SBP>200mmHg) in the phaeochromocytoma group: transient episodes (n=5), transient with persistent episodes (n=1), persistent episode (n=1). One experienced a transient SBP >220mmHg. The main catecholamines secreted were:

norepinephrine, epinephrine and dopamine (n=3), norepinephrine and epinephrine (n=3) and norepinephrine (n=1). These episodes were all controlled with phentolamine and labetalol. All patients who experienced severe hypertension were diagnosed with preoperative hypertension. Two patients in the non phaeochromocytoma group experienced SBP>200mmHg: transient episode (n=1), transient with persistent episodes (n=1). The patients had Cushing's syndrome and a cortisol producing adrenocortical carcinoma (respectively). Intraoperative antihypertensive use was significantly increased in the phaeochromocytoma group (Table 5.3). Two patients in the phaeochromocytoma group developed a persistent sinus tachycardia. These episodes were treated successfully with labetalol. One patient with a non functioning adenoma developed a cardiac arrhythmia. There was no significant difference between groups for persistent hypotensive episodes. The intraoperative fluid requirement was not different between the two groups (p=0.114) (Table 5.3).

Recovery room data

There were no persistent haemodynamic changes in the recovery room. Recovery room haemodynamic data is shown in Table 5.4. Two patients experienced transient hypotension (SBP<80mmHg) after phaeochromocytoma resection. One of these patients was treated with metaraminol. There was no perioperative mortality.

Table 5.4 Table to show recovery room haemodynamic parameters between patients with phaeochromocytomas and non phaeochromocytomas

Recovery room parameters	Phaeo (number of operations=40)	Non Phaeo (number of operations=119)	P value
Transient Hypotension (SBP<80mmHg)	2	2	0.564
Vasopressor treatment	1	0	0.566
Discharge pulse†	75 (70-80)	75 (65-85)	0.984
Discharge SBP (mmHg)†	114 (105-126)	130 (120-145)	<0.005

SBP=systolic blood pressure, at time of discharge from recovery
HR=heart rate, at time of discharge from recovery
† Values are median (interquartile range)

5.4 Discussion

Laparoscopic adrenalectomy for phaeochromocytoma was associated with increased episodes of severe intraoperative hypertension when compared to the laparoscopic resection of other adrenal tumours. These episodes were all controlled with anti-hypertensive medication. There were no other significant differences in terms of hypotensive episodes, cardiac arrhythmias or intravenous fluid requirements.

Phenoxybenzamine (a long acting, noncompetitive α adrenergic antagonist) has been the mainstay of preoperative treatment inhibiting the effects of excessive catecholamines during phaeochromocytoma resection (Bravo & Tagle, 2003). The pharmacological half life for phenoxybenzamine is about 24 hours. In an attempt to prevent prolongation of α blockade in the post-operative period, oral phenoxybenzamine is usually stopped 24-48 hours before surgery. Despite the documented benefits of oral phenoxybenzamine, severe intraoperative hypertension (SBP >200mmHg) can still occur. (Kinney et al., 2000), used only preoperative oral phenoxybenzamine, without an infusion the day before admission, in 127 out of 143 patients undergoing phaeochromocytoma resection. 20 patients (14%) experienced very severe SBP >220mmHg (mean 9±9min). 117 out of 143 patients required intra-operative antihypertensive treatment. LA was only performed in 3% of patients.

In our study, phenoxybenzamine was administered as an oral preparation in the phaeochromocytoma group at time of diagnosis. Unlike other studies, all the patients in the group received an intravenous preparation of phenoxybenzamine (1mg kg^{-1}) the day before surgery. Using this regimen, there were no differences in terms of preoperative pulse and systolic blood pressure measurements between the two groups. Only one patient in the phaeochromocytoma group experienced transient very severe intraoperative hypertension (SBP >220mmHg <10 minutes). It is interesting to note that 6 of the 7 patients in the phaeochromocytoma group who experienced severe intraoperative hypertension had elevated

levels of both epinephrine and norepinephrine. This would suggest that the more problematical patients are those with a mixture of high alpha and beta agonism. Our regimen of comprehensive alpha blockade prevented persistent severe hypertension in all those secreting only norepinephrine. This would support the use of alpha antagonists as being the primary mechanism to modify, but there also needs to be attenuation of the extra alpha and beta agonism which results from epinephrine.

A previous series demonstrated that pre-treatment with phenoxybenzamine prior to phaeochromocytoma resection resulted in persistent α-adrenoceptor blockade well into post operative period (Prys-Roberts & Farndon, 2002). After resection, this resulted in persistent arterial hypotension resistant to adrenergic arteriolar constrictors and large volumes of intravascular fluid. In an attempt to reduce post operative hypotension, Prys-Roberts et al. changed to a specific α1-adrenoceptor antagonist, doxazosin, instead of phenoxybenzamine, because it does not block presynaptic α2 mediated release of norepinephrine. The authors felt, there was no detectable adrenergic blockade in 25 patients receiving doxazosin (4mg/day) on the first postoperative day.

Our series demonstrated no patient in the phaeochromocytoma group experienced persistent hypotension (systolic blood pressure <80mmHg >10 minutes) in the recovery room period. There was also no significant difference between groups for intraoperative intravenous fluid. Fluid balance assessment, fluid replacement therapy and intraoperative blood loss have improved since the series by Prys-Roberts, therefore relative hypovolaemia and hypotension should be less of a problem.

The use of preoperative calcium antagonists as an alternative to phenoxybenzamine has been advocated to control blood pressure and symptoms for patients undergoing phaeochromocytoma resection (Lebuffe et al., 2005)(Proye et al., 1989). This regimen attempts to prevent the adverse effects of the prolonged α-blockade of phenoxybenzamine.

(Lebuffe et al., 2005) used a preoperative regimen of oral nicardipine as an alternative to phenoxybenzamine for phaeochromocytoma resection, they reported 27 out of 105 patients (26%) experienced a severe SBP > 200 mmHg, 12% experienced persistent hypotension and 30% experienced a tachycardia (heart rate >120bpm). Only 22% of procedures were performed laparoscopically. These results have not demonstrated an improvement in the perioperative haemodynamic stability compared to our current series.

Few series have compared perioperative haemodynamic changes for LA for phaeochromocyotma with LA for other adrenal tumours. (Gotoh et al., 2002), compared 9 patients undergoing LA for phaeochromocytoma with 28 patients undergoing LA for other adrenal tumours. In this study, hypertensive episodes were documented for the phaeochromocytoma group but not for the other adrenal tumours. In another recent study, (Weismann et al., 2006), compared 27 patients undergoing LA for phaeochromocytoma with 28 patients undergoing LA for other tumours. For the phaeochromocytoma group, there were increased episodes of SBP>200mmHg with increased anti-hypertensive use, more episodes of tachycardia and hypotension. None of the patients received a phenoxybenzamine infusion and data on preoperative oral phenoxybenzamine usage was incomplete. Suitability for laparoscopic phaeochromocytoma resection was highly selective. Patient selection was not consecutive. Therefore, haemodynamic comparisons in these studies should be reviewed with caution.

In the present study, all patients received an infusion of phenoxybenzamine the day before surgery and the only contraindication to the laparoscopic approach was adrenal tumour local invasion. Persistent hypertensive episodes were more frequent in the phaeochromocytoma group (similar to Weissmann et al) but there were no other perioperative haemodynamic differences between groups.

We agree with other authors (Kinney et al., 2000)(Kercher et al., 2002)(Cheah et al., 2002), that the marked improvement in morbidity and mortality in phaeochromocytoma resection since the 1950s is attributed to a number of factors: experienced endocrine, anaesthetic, surgical team, improved pre and perioperative pharmacological treatment for hypertension and arrhythmias, improved tumour localisation and improved surgical technique.

Conclusion

This study has demonstrated, in the presence of an experienced multidisciplinary team and complete preoperative alpha blockade, laparoscopic adrenalectomy for phaeochromocytoma can be accomplished with low perioperative haemodynamic complications.

6. The role of laparoscopic adrenalectomy for adrenal tumours of 6cm or greater

6.1 Introduction

Since it was introduced in 1992(Gagner et al., 1992), laparoscopic adrenalectomy (LA) has become the procedure of choice for most adrenal pathologies. It is uncertain if the laparoscopic resection of large (≥6cm) potentially malignant adrenal tumours is appropriate due to concern over incomplete resection and local recurrence (Henry et al., 2002)(Walz et al., 2005)(Schell et al., 1999)(Pisanu, Jafari, Pattou, Carnaille, & Proye, 2001)(Valeri et al., 2001). For this reason, selection of those suitable for laparoscopy is practised by many surgeons and this may bias outcomes. Therefore the favourable results of LA for large adrenal tumours in previous published series should be interpreted with caution.

The aim of the present study was to compare the outcomes of LA for tumours ≥6cm with those <6cm from a consecutive series of patients where selection was practised infrequently. The only contraindications to the laparoscopic approach, in the present series, were radiological locally advanced adrenal tumours requiring en-bloc resection of adjacent organs or the requirement of an additional open procedure.

6.2 Methods

Details of all patients referred with adrenal tumours between January 1999 and January 2009 were recorded prospectively on a database. Preoperative, intraoperative and postoperative data were obtained from retrospective case note review.

All patients were assessed preoperatively by the endocrine unit as previously described (Introduction 1.4.2).

The adrenal tumours were imaged using computed tomography (CT) and/or magnetic resonance imaging (MRI). Maximum diameter of the adrenal tumour was then measured.

A diagnosis of possible adrenal carcinoma was based on the patient history and radiology findings. Morphology appearances which suggest malignancy may include: increased size (≥6cm), large necrotic areas, increased heterogeneity, irregular borders and local invasion.

The only contraindications to LA were locally invasive adrenal mass on CT or MRI or the requirement of an additional open surgical procedure. If the adrenal local invasion involved only the kidney a LA and en-bloc nephrectomy was performed.

Preoperative information included age, sex, diagnosis and co-morbidity. Intraoperative information included total anaesthetic time, requirement of blood products and operative complications. Postoperative information included complications, intensive care admissions, length of hospital stay, histopathology and tumour size. Any evidence of tumour recurrence or mortality on follow up was also recorded to July 2009. Therefore the operative outcomes of adrenal tumours ≥6cm versus those <6cm could be compared.

Statistical analysis

Categorical variables were compared using Chi-square test. Continuous data are presented as

median and interquartile ranges (IQR) and analysed with the Mann-Whitney test. A p value of

<0.05 was assumed to be significant. Analyses were performed using SPSS (Version 17.0).

6.3 Results

Characteristics of patients referred with adrenal tumours

During the ten year period 180 patients were referred for adrenalectomy. Figure 6.1 illustrates the outcome of patients referred for adrenalectomy.

Figure 6.1 Outcome of patients referred for adrenalectomy
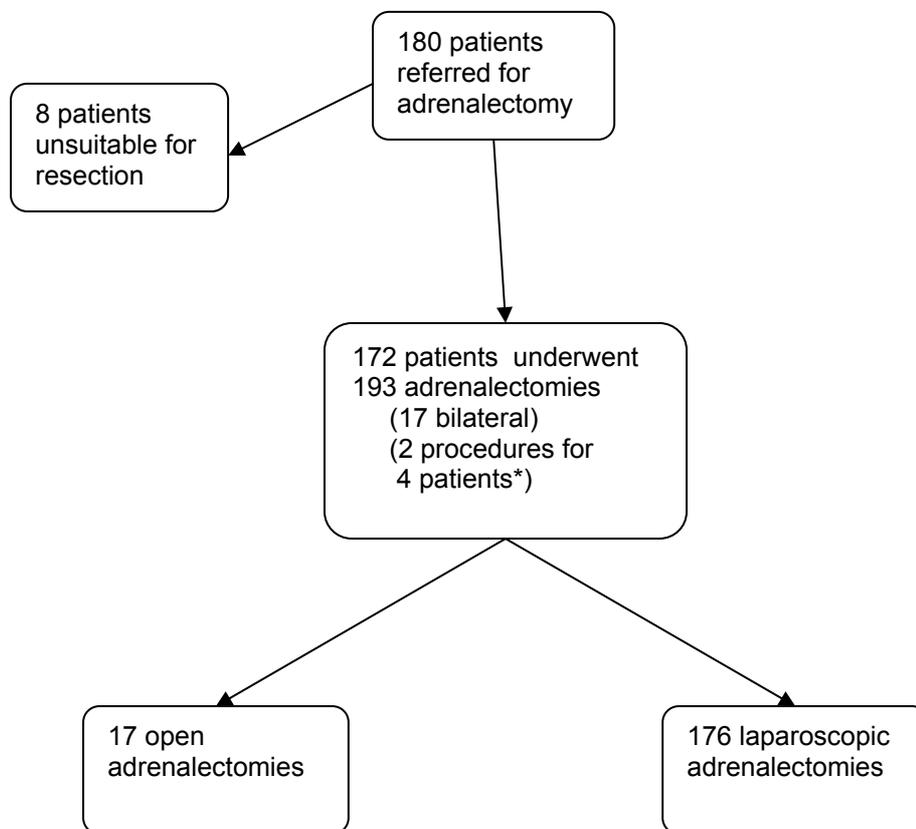
* One patient had further debulking of recurrent adrenocortical carcinoma, 3 patients had asynchronous adrenalectomy because of further adrenal gland pathology [Cushing's syndrome (n=2), phaeochromocytoma (n=1)].

Eight patients were deemed unsuitable for resection: unfit for resection (n=3), metastatic adrenocortical carcinoma (n=4) and one patient with a small (1 cm) non functioning adenoma.

172 patients underwent 193 adrenalectomies (17 bilateral, 4 delayed contralateral adrenalectomies). Indication for bilateral adrenalectomy included: Cushing's disease (n=11), phaeochromocytoma (n=4), and isolated adrenal metastasis (n=2). Indication for the 4 delayed

contralateral adrenalectomies are given in Figure 5.1. There were 176 laparoscopic adrenalectomies and 17 open procedures. Characteristics of patients undergoing LA are shown in Table 6.1.

Table 6.1 Characteristics of patients undergoing laparoscopic adrenalectomy

Characteristics	
Number of patients	156
Number of adrenalectomies	176
Sex ratio (M:F)	66:90
Age*	57 (47-65)
Tumour site	
Left	72
Right	70
Bilateral	17
Indication for referral[a,b]	
Conn's adenoma	38
Phaeochromocytoma	44
Cushing's syndrome	25
Cushing's disease	9
Non functioning adrenal tumour	8
Suspected adrenal carcinoma	20
Suspected adrenal metastasis	12
Mixed secreting adenoma	2
Adrenal cyst	1

*Values are median (IQR)

Operative data

Operative data for laparoscopic procedures are shown in Table 6.2.

Table 6.2 Intraoperative outcome

	Tumours ≥6cm	Tumours <6cm	P value

	(operations=62)	(operations=97)	
Total anaesthetic time for unilateral LA (mins)*	120 (90-145)	100 (80-125)	0.039
Conversions	6	2	0.077
Operative complications			
Blood loss (>500mls)	6	2	0.077

* Values are median (IQR)

69 out of 176 LA were performed for patients with a maximum tumour diameter measuring 6 cm or more. The median total anaesthetic time for large adrenal tumours (≥6cm) was significantly longer compared to smaller adrenal tumours (<6cm) (120 minutes [IQR 90-145] versus 100 minutes [IQR80-125]; P=0.039).

3 patients had LA with en-bloc nephrectomy: suspected local invasion (n=2) or renal carcinoma with bilateral adrenal metastases (n=1). Pathology showed: adrenocortical carcinoma (n=2) and clear cell renal carcinoma with bilateral adrenal metastases.

Conversion to an open procedure was necessary for 8 patients. 6 conversions were for patients with tumours ≥ 6cm. 3 were converted due to concern over adjacent structure invasion. One patient undergoing combined adrenalectomy and nephrectomy for presumed adrenocortical carcinoma was converted due to splenic bleeding (blood loss, 600mls), open splenectomy was required. One patient undergoing bilateral adrenalectomy for Cushing's disease was converted on the right side due to adhesions after a previous open cholecystectomy. The other patient with a possible phaeochromocytoma on preoperative assessment (catecholamines upper limit

of normal) was converted because the tumour was found to originate from the kidney and therefore a radical nephrectomy was performed. There were 2 conversions for tumours <6cm: one to achieve haemostatic control after an adrenal vein tear and the other due to dense adhesions to liver and colon after previous ipsilateral nephrectomy.

For patients with adrenal tumours ≥6cm, 6 had a blood loss >500mls. 3 out of the 6 were for converted patients (n=2) or simultaneous laparoscopic nephrectomy (n=1). The remaining 3 were for patients with phaeochromocytoma. For patients with adrenal tumours <6cm, 2 had blood loss >500mls. One was for a patient with bilateral phaeochromocytoma and multiple friable vessels and the other was for bleeding from a left renal vein. Haemostasis was achieved laparoscopically in both patients. No patient required intraoperative blood transfusion.

All patients undergoing LA had clear resection margins.

Postoperative data

The median post-operative stay (which included patients converted to open) for patients undergoing LA for tumours ≥ 6cm was significantly different from tumours<6cm (3 days [IQR 2-5] versus 2 days [IQR2-3]; P<0.005) (Table 6.3).

Table 6.3 Postoperative outcome

	Tumours ≥6cm (operations=62)	Tumours <6cm (operations=97)	P value
Post operative complications			
Arrhythmia	1	0	
Pneumonia	5	2	
Subphrenic collection	1	1	
Port site bleed	0	1	
Wound infection (In hospital)	1	3	
Acute renal failure	1	1	
Pulmonary embolism	0	1	
Urinary tract infection	1	0	
Total complications	10	9	0.295
Post operative stay (days)* (includes those converted to open)	3 (2-5)	2 (2-3)	< 0.005

* Values are median (IQR)

Out of the 159 laparoscopic procedures performed, there was no significant difference for complications between the 2 groups (10 (≥6cm) versus 9 (<6cm); P=0.295). Laparoscopic complications between the two groups are summarised in Table 6.3. There were no post-operative mortalities after laparoscopic adrenalectomy.

Follow up

For patients undergoing LA, the median follow up was 41 months [IQR 22-76]. In this time there have been no clinical or radiological evidence of local recurrence for patients undergoing LA. 3 patients have developed metastatic disease. One has diffuse intrabdominal disease 5 years after the complete laparoscopic resection of a 5cm phaeochromocytoma. The other 2 patients have developed distant metastatic disease after laparoscopic resection of large (>6cm) adrenocortical carcinomas. There have been 6 cancer related deaths after LA: 2 after resection of adrenal metastasis (metastatic melanoma (n=1), metastatic neuroblastoma (n=1), one with B-cell lymphoma, one with an unrelated metastatic adenocarcinoma (previously resected phaeochromocytoma), one with pulmonary metastasis after resection of adrenocortical carcinoma and the other from metastatic medullary thyroid carcinoma (previous bilateral phaeochromocytomas in a patient with MEN type 2b).

6.4 Discussion

Out of the 176 laparoscopic adrenalectomies performed, 69 (39%) were for adrenal masses ≥6cm. There were increased conversions in this group, mainly for concern over local tumour

invasion. Post operative stay for patients with adrenal tumours ≥6cm was a day longer compared to those <6cm (3 days versus 2 days). After a median follow up of 41 months, there has been no clinical or radiological evidence of local recurrence in any patient that has had an attempted laparoscopic approach.

Adrenal masses ≥6cm are generally regarded as having a high risk of malignancy. Therefore many surgeons do not attempt LA for large adrenal tumours due to concern over incomplete resection and local recurrence. However, an increasing number of series have demonstrated the safety of this approach together with low rates of local recurrence (Table1.6). But, the percentage of patients with tumours ≥6cm was significantly lower than our series suggesting selection bias. For example only 7% (33 out of 429) of LA were for large adrenal tumours in a series by (Walz et al., 2005) . This was also illustrated by (MacGillivray et al., 2002), 20% (12 out of 60) of LA were performed for large adrenal tumours. Henry et al demonstrated excellent results for laparoscopic resection of possible malignant tumours in 19 patients (Henry et al., 2002). However these patients were selected from a series of 233 LA. Similar outcomes were achieved by Palazzo et al but again only 5% (19 out of 391) of LA were for tumours ≥6cm (Palazzo et al., 2006). Ramacciato et al, reported the experience of LA for adrenal tumours > 7cm (Ramacciato et al., 2008). 18 out of 107 patients had LA for adrenal mass >7cm. Complications were low and there were no cases of incomplete resection or local recurrence. There was no mention of selection criteria for laparoscopy or the number of patients requiring an open procedure. Therefore, due to the selection bias that may exist in these series the encouraging results should be reviewed with some caution.

Unlike these series, the present study included all patients referred with adrenal tumours and a significant higher percentage (43%) had large tumours with the majority (80%) undergoing attempted laparoscopic resection. Selection for laparoscopy has remained constant in the 10 year study period. 3 patients underwent LA with en-bloc nephrectomy with low morbidity and

good oncological outcome. In patients with local invasion into structures other than kidney we feel, like other series, an open approach for these tumours provides the best chance of complete resection and allows vascular control of major vessels when required.

Mean conversion rate for selected large series has been reported as 3.6%. Conversion was slightly higher in the present series (4.5%). The reasons for lower number of conversions in other series may include: selection for those suitable for laparoscopy changed dramatically over time or laparoscopic resection of large adrenal tumours was not practised.

Although not statistically significant, there were more conversions for adrenal tumours ≥6cm compared to those <6cm (10% versus 2%). The main reason for the difference was concern over local invasion for patients with larger adrenal tumours. We feel the open technique allows the best chance to achieve complete resection in these cases.

Radiological assessment of tumour size can be used to predict the likelihood of malignancy. In a risk assessment study of 457 adrenal cortical carcinomas, (Sturgeon et al., 2006), reported a four fold increase in malignancy for adrenal tumours ≥6cm. In the current series, out of 69 LA performed for tumours ≥ 6cm, 10 had a histological diagnosis of adrenal cortical carcinoma based on the Weiss criteria. Adrenal resection for these patients was complete without evidence of local recurrence after a median follow up of 41 months. This compares very favourably with other studies who document the mean disease free interval for adrenal cortical carcinoma, even after a curative operation, is approximately 12-22 months. We feel like other authors, adopting a policy of LA only for tumours <6cm or highly selecting those with tumours >6cm would prevent a large number of patients receiving the benefits of the laparoscopic approach. Even in the presence of malignancy, we have shown laparoscopic resection can

achieve very favourable oncological outcomes after long-term follow-up. The laparoscopic approach gives an excellent view of large tumours and radical resection with a low blood loss can be performed without the need for large abdominal or thoracoabdominal incisions in these patients.

LA for non-invasive very large masses (≥ 10cm) has been described (Ramacciato et al., 2008)(Shen, Kebebew, Clark, & Duh, 2004)(Gagner et al., 1997). There were 9 patients with adrenal tumours ≥ 10cm in this series. Authors have commented on the difficulty in mobilisation, tedious dissection and limited working space (Assalia & Gagner, 2004). Despite this, in the current series, we felt laparoscopic mobilisation of these very large adrenal tumours would allow the benefits of a smaller targeted incision to remove the specimen rather than the morbidity associated with a large subcostal or thoracoabdominal incision from the outset. The favourable outcome of this approach has been demonstrated in terms of low postoperative morbidity, hospital stay (median of 4 days) and favourable oncological outcomes.

An alternative laparoscopic assisted approach has been described for these very large tumours. (Shen et al., 2004) have described the utilisation of a hand port for adrenal masses that cannot be completed laparoscopically. The authors used a hand assist device (Pneumo-Sleeve, Dexterity Surgical; or Lap Disk, Ethicon) inserted as a 6-8cm subcostal incision. The hand assist device was used successfully in 4 out of the 261 LA: large (>15cm) masses (n=2) and concern over local invasion (n=2). The device was reported to facilitate dissection and help detect evidence of local invasion. However, no difference in terms of complications or hospital stay was detected between hand assist and the open converted procedures. The authors acknowledge larger numbers of patients are required before differences would become apparent. Although the hand assist device was not used in the present series, we believe this

technique is an alternative in situations with very large (>10cm) adrenal masses or concern over local invasion.

In the absence of local invasion, this study has shown the oncological outcome and postoperative morbidity of laparoscopic adrenalectomy for patients with tumours ≥6cm was comparable to those with tumours <6cm. Post-operative stay was a day longer (3 rather than 2 days). Concern over incomplete resection and local recurrence for these large adrenal tumours has not been realised. This series has helped confirm a policy of initial laparoscopic resection for all non-invasive adrenal tumours can be applied safely. This would prevent patients undergoing unnecessary open procedures and allow the benefits of laparoscopy.

7 The role of open adrenalectomy in the laparoscopic era

7.1 Introduction

Many case series have reported the success of laparoscopic adrenalectomy (LA) for the majority of adrenal pathologies. However, the true incidence and outcomes of patients

undergoing open adrenalectomy (OA) within these series were unclear. Reasons include: failure to report details of those undergoing OA or the role of laparoscopy has expanded over time to include large potentially malignant tumours.

The current study aimed to look at the outcome of patients undergoing OA in a consecutive series of patients where selection for LA was constant during a 10 year period.

7.2 Methods

From January 1999 to January 2009, details of all patients referred for adrenalectomy were recorded prospectively on a database. Analysis was performed retrospectively.

Prior to starting laparoscopic adrenalectomy in January 1999, laparoscopic experience included: cholecystectomy, nephrectomy and colonic resection. A sound knowledge of the retroperitoneal anatomy had also been achieved by regular resection of abdominal sarcomas.

All patients were assessed preoperatively by the endocrine unit. The adrenal tumours were imaged CT and/or MRI.

LA was performed using the lateral transabdominal approach as described and illustrated in the Introduction (1.8.3). Techniques for open adrenalectomy are described in the Introduction (1.8.7). Indicators for open adrenalectomy were locally invasive adrenal mass or the requirement of an additional open surgical procedure.

Data on in-hospital perioperative outcomes, follow-up (local recurrence, distant metastatic disease and post operative endocrine function) were collected.

Statistical analysis

Categorical variables were compared using Chi-square test. Continuous data are presented as median and interquartile ranges (IQR) and analysed with the Mann-Whitney test. A p value of <0.05 was assumed to be significant. Analyses were performed using SPSS (Version 17.0).

7.3 Results

Preoperative

During the ten year period 180 patients were referred for adrenalectomy. Figure 6.1 illustrates the outcome of patients referred for adrenalectomy. 172 patients underwent 193 adrenalectomies. There were 176 laparoscopic adrenalectomies and 17 open procedures. The indications for the 17 open procedures were: local invasion (n=8), requirement of an additional open procedure (n=3), recurrent adrenal tumour (n=2), previous radical retroperitoneal lymphadenectomy (testicular teratoma) (n=1), sarcoma arising from adrenal (n=1), preoperative diagnosis of sarcoma (final diagnosis phaeochromocytoma) (n=1) and the emergency resection of a large (12cm) phaeochromocytoma (unable to adequately control blood pressure in the intensive care unit). Characteristics of patients undergoing OA are shown in Table 7.1.

Table 7.1 Characteristics of patients undergoing open adrenalectomy

	Open adrenalectomy
Number of patients	16
Number of adrenalectomies	17
Sex ratio (M:F)	10:6
Age*	60 (43-72)
Tumour site	
Left	5
Right	12
Indication for referral	
Phaeochromocytoma	3
Non functioning adrenal tumour	1
Suspected adrenal carcinoma	9
Recurrent adrenal carcinoma	1
Suspected adrenal metastasis	1
Adrenal sarcoma	2

*Values are median (IQR)

Operative data

Operative data for adrenalectomies are shown in Table 7.2.

Table 7.2 Operative outcomes comparing open and laparoscopic adrenalectomy

	Open adrenalectomy (operations=17)	Laparoscopic adrenalectomy (operations=159)	P value
Total anaesthetic time for unilateral adrenalectomy (mins)*	150 (120-195)	110 (85-135)	<0.005
Structure resection due to local invasion			
Inferior vena cava	1 (tumour thrombus)	-	
Kidney	4	5	
Diaphragm	1	-	
Colon	1	-	
Liver	1	-	
Spleen	1	1	
Blood loss (>500mls)	13	8	<0.005

* Values are median (IQR)

The total anaesthetic time for OA was significantly longer than LA. The open procedures were often complex procedures associated with significant greater blood loss and increased requirement for en-bloc resection of adjacent structures due to local invasion (Table 7.2). 2 patients required thoraco-abdominal procedures to allow adequate access. One patient with an adrenocortical carcinoma had inferior vena cava exploration to excise tumour thrombus.

2 patients had incomplete resection following open procedures: adrenal cortical carcinoma (n=1) and sarcoma originating from the adrenal (n=1).

Postoperative data

Table 7.3 summarises the postoperative outcomes. The median post-operative stay for patients undergoing OA was significantly longer compared to those undergoing LA.

Table 7.3 Post-operative outcomes comparing open and laparoscopic adrenalectomy

	Open adrenalectomy (operations=17)	Laparoscopic adrenalectomy (operations=159)	P value
Post operative complications			
Arrhythmia	-	1	
Pneumonia	3	7	
Subphrenic collection	2	2	
Port site bleed	-	1	
Wound infection (In hospital)	2	4	
Acute renal failure	2	2	
Pulmonary embolism	-	1	
Urinary tract infection	1	1	
Small bowel fistula	1	-	
Total complications	11	19	<0.005
Mortality	1	-	
Post operative stay (days)*	9 (6-19)	3 (2-4)	<0.005

* Values are median (IQR)

One patient undergoing open adrenalectomy died in the early postoperative period. The adrenal pathology was a non-functioning adenoma and was performed open because a synchronous left hemicolectomy was required for complicated diverticular disease. In the early postoperative period, the patient developed a perforated peptic ulcer (subsequently oversewn) and then died due to multi-organ failure.

Follow-up

For patients in the OA group, after a median follow-up of 65 months (IQR 20-87), there have been 6 local recurrences: adrenocortical carcinoma (n=4) and spindle cell sarcoma originating from adrenal gland (n=2). One patient with recurrent adrenocortical carcinoma underwent a repeat resection with en-bloc nephrectomy. This patient has subsequently developed liver metastasis. 2 patients with adrenocortical carcinoma have died. Both patients developed distant metastases and local recurrence.

3 patients undergoing open adrenalectomy for phaeochromocytoma have had no evidence of recurrence, metastatic disease or catecholamine excess.

7.4 Discussion

Out of the 193 consecutive adrenalectomies, 17 (9%) were performed as an open procedure. The main reason for OA was evidence of local invasion on pre-operative imaging (8 out of 17). This was confirmed at laparotomy and was associated with adjacent structure resection. 6 patients had evidence of local recurrence on follow-up.

Since LA was introduced in 1992, many series have reported the success of LA in consecutive series of patients. In these series it has been difficult to interpret the true incidence or outcomes of patients undergoing OA as selection for laparoscopy changed over the time period or the open data was not reported. (Soon et al., 2008), in a series of 177 adrenalectomies performed 26 OA (15%). But did not give any details about which patients were suitable for laparoscopy. In another series (Palazzo et al., 2006) documented the results of a large series of adrenalectomies. Over a 10 year period, out of 462 adrenalectomies, 71 were open (15%). OA was performed when malignancy was suspected on preoperative imaging. Out of the 71 OA, no outcome data was available. The outcome of patients undergoing OA within a laparoscopic series remains largely unknown.

In the present series the selection of patients for open adrenalectomy remained unchanged in the 10 year period. Using these criteria, the number of OA was lower (9%) compared to other series. The main reason for open procedure (8 out of 17) was concern over local invasion. Other reasons included previous extensive retroperitoneal dissection, recurrent tumour or suspected retroperitoneal sarcoma. The patient outcomes were often associated with high blood loss and prolonged hospital stay.

Malignancy is highly suspected in the presence of local invasion by CT or MRI. In this situation, we agree with other authors that the requirement of extensive en-bloc resection of invaded organs is best performed by the open approach (Henry et al., 2002). The present series shows

the extensive dissection required including adjacent structure involvement: kidney, liver, spleen, colon and inferior vena cava. We have shown in Chapter 5 in the absence of local invasion LA can be performed safely with good oncological outcome and postoperative recovery.

Adrenocortical carcinoma has a poor prognosis with 5 year survival rates varying from 16-38% (Vassilopoulou-Sellin & Schultz, 2001). Surgery remains the only potential for cure. For patients who have had potentially curative surgery local recurrence rates of 20-30% have been reported. This compares with our series, out of 15 patients with adrenocortical carcinoma, 4 have had a local recurrence. These all occurred in the open group. One patient with local recurrence has had repeat resection. This is an accepted option for patients with recurrent disease and has been associated with improved survival (Bellantone et al., 1997).

In summary, we have demonstrated with an appropriate experienced team consisting of surgeons, anaesthetists, radiologists and endocrinologists, laparoscopic resection can be attempted safely with low morbidity in the majority (92%) of patients deemed suitable for adrenalectomy. Open adrenalectomy when indicated (mainly for local invasion) was a demanding procedure associated with resection of adjacent structures and high local recurrence rates.

8 Laparoscopic adrenalectomy for isolated adrenal metastasis

8.1 Introduction

Resection of isolated adrenal metastasis (AM) has been reported to prolong survival when compared to patients who have had non-operative management (Kim, Brennan, Russo, Burt, & Coit, 1998a) (Luketich & Burt, 1996)(Sarela, Murphy, Coit, & Conlon, 2003).

Laparoscopic adrenalectomy (LA) has become the procedure of choice for the majority of adrenal pathologies.

However, only a few series have focussed on the role of LA for isolated AM. (Strong et al., 2007) in one of the largest series of 94 adrenalectomies for isolated AM compared the results of LA to open adrenalectomy. This showed improved recovery with similar oncological results for LA patients. However, selection for laparoscopy was practised in that the mean size of tumour was 3.8cm in the LA group compared to 6.4cm for the open group. Therefore, the favourable results for laparoscopy in this select group of patients may not hold true for patients with larger adrenal masses.

The aim of the present study was to evaluate the results of LA for isolated AM in a consecutive series of patients where the only contraindication to laparoscopy was local invasion on preoperative imaging.

8.2 Methods

From January 1999 to January 2009, details of all patients referred for adrenalectomy were recorded prospectively on a database.

A diagnosis of suspected adrenal metastasis was based on clinical history and CT or MRI findings. Indications for adrenalectomy were curative intent for solitary adrenal metastasis and diagnostic intent for suspected adrenal metastasis.

A metachronous metastasis was defined as adrenal metastasis appearing ≥6 months after initial diagnosis.

Data on in-hospital outcomes, follow-up and mortality were collected by case note review.

8.3 Results

Out of the 176 LA, 12 patients were suspected as having isolated adrenal metastasis. Median age was 61 (interquartile range (IQR) 54-73). There were 9 males and 3 females. No patient had a preoperative adrenal biopsy.

Patient characteristics are summarised in Table 8.1. 11 patients presented with metachronous AM and 1 patient presented with synchronous AM. 9 of the 12 patients presented with AM of suspected renal cell carcinoma origin. Of the 8 patients with suspected metachronous renal origin metastasis, 4 were ipsilateral AM.

Table 8.1 Patient characteristics with isolated adrenal metastasis

Patient	Primary tumour	S/M	Side	Size (mm)	Conversion	TAT (mins)	Hospital stay (days)	Pathology	Follow-up	Status
1	Kidney	S	Bilat	Right 72 Left 70	-	305	14	AM	23	ANED
2	Melanoma	M	Left	90	-	120	3	AM	13	DOFD
3	Kidney	M	Left	70	-	80	3	AM	16	AWD
4	Olfactory neuroblastoma	M	Bilat	Right 80 Left 70	-	195	2	AM	45	DOFD
5	Kidney	M	Right	40	yes	140	17	AM	7	AWD
6	Kidney	M	Right	27	-	75	2	AM	21	AWD
7	Kidney	M	Left	32	*	120	60	AM	26	ANED
8	Kidney	M	Left	40	-	120	3	AM	16	ANED
9	Kidney	M	Left	20	-	65	3	AM	12	ANED
10	Kidney	M	Left	40	-	105	3	AM	9	ANED
11	Kidney	M	Right	20	-	200	3	Adenoma	11	AWD
12	Unknown	M	Left	17	-	110	2	Adrenal gland necrosis	81	ANED

S: synchronous; M: metachronous
* Patient underwent laparoscopic distal pancreatectomy and splenectomy due to concern over local invasion
 TAT: total anaesthetic time
AM: adrenal metastasis
AWD: alive with disease, ANED: alive with no evidence of disease, DOFD: dead of disease

All patients underwent initial LA. The median total anaesthetic time for unilateral LA was 115 (IQR80-125). There was one conversion for an ipsilateral right metachronous renal origin AM due to dense adhesions involving colon, liver and inferior vena cava. Another patient with an ispilateral left AM underwent an en-bloc laparoscopic distal pancreatectomy and splenectomy due to concern over local invasion.

There were 3 post-operative complications: left upper quadrant collection in the patient with local invasion to spleen and pancreas, pneumonia in the converted patient and a urinary tract

infection in another. Hospital stay was 60, 17 and 14 days respectively in these patients. For other patients the hospital stay ranged from 2-3 days.

On histological examination there were no cases of incomplete adrenal resection. 2 patients did not have evidence of adrenal metastatic disease.

After a median follow-up of 16 months (IQR 11-25), 2 patients have died due to disseminated disease (metastatic melanoma (n=1) and metastatic olfactory neuroblastoma (n=1). All 9 patients with renal origin AM were alive after follow-up. Of the 9, 4 are alive with disease (lung metastasis (n=2), lymph node metastasis (n=2)).

8.4 Discussion

In a highly select group of patients, surgery for isolated AM has been shown to improve survival. It is not clear if laparoscopic adrenalectomy results in less morbidity or worse oncological outcome compared to open adrenalectomy for these patients. In the current study, we report our experience of LA in patients with suspected isolated AM. Over the 10 year period, 12 out of 176 LA were for suspected isolated AM. LA was associated with low morbidity and short hospital stay [median 3 days (IQR2-11)]. All adrenal masses were completely resected and there has been no evidence of local recurrence on follow-up. All patients with renal origin AM were alive in the follow-up period.

Other series have reported the experience of LA for isolated AM. (Sebag et al., 2006), reported the experience of 16 LA for AM. The mean hospital stay was 5 days with minor complications occurring in 3 patients. The authors felt LA gave an acceptable oncological outcome with improved recovery when compared to open surgery. Indicators for laparoscopy or open surgery were not given. (Bonnet et al., 2008) reported the outcome of 8 LA for metachronous metastasis from renal cell carcinoma. There were no post-operative complications and the median hospital stay was 3 days. The series reported excellent disease-free survival of 87% after 39 month follow-up. LA was not performed for large masses (>10cm). In a large series, (Strong et al., 2007) compared 31 LA versus 63 open adrenalectomies (OA) for isolated AM. The authors found LA gave equivalent oncological results to OA but laparoscopy allowed improved recovery with lower morbidity. However, the results should be interpreted with caution as the patients in the open group had larger adrenal masses (6.4cm for OA versus 3.8cm for LA).

In the present study the only contraindication to laparoscopy was a locally invasive adrenal mass on preoperative imaging. Using these criteria for laparoscopy, we report similar encouraging results in terms of complications and hospital stay after LA for isolated AM compared to other series. LA for renal origin AM appeared to have the best outcome, in

agreement with Bonnet and colleagues. LA for other AM, in our series, was associated with a dismal prognosis. It is difficult to draw any conclusions from this as there were only 2 patients with AM from primaries other than renal cell carcinoma.

We know once a patient has a diagnosis of an extraadrenal malignancy, the chance that an incidentally detected adrenal mass is malignant increases substantially (Young, 2007). Therefore, unless a lesion on CT or MRI conforms to strict criteria for benignity, AM should be strongly considered. We used similar criteria to Bonnet and colleagues, LA was considered in any patient with known extraadrenal malignancy and an isolated adrenal lesion >2cm or an adrenal mass increasing in size on serial imaging. In the current series, using these criteria, 10 out of 12 patients confirmed the diagnosis of AM. One patient with suspected bilateral AM had no history of extraadrenal malignancy. AM was suspected as the patient had bilateral necrotic adrenal masses (CT scan performed for unrelated pathology). A diagnostic unilateral adrenalectomy was performed and pathology showed adrenal gland necrosis only.

In the current series, there were 3 patients with ipsilateral metachronous renal origin AM. All procedures were technically difficult due to adhesions. 2 were performed without complication. The other was converted due to dense adhesions involving liver, IVC and colon. We agree with Bonnet et al that LA for ipsilateral metachronous renal origin AM, although feasible, were all technically more demanding.

In conclusion, we have shown in a highly selected population LA can be performed with low morbidity and good oncological outcomes for the majority of patients with isolated renal origin AM. Patients with isolated AM from other sites appeared to have a much worse prognosis on follow-up. However, larger patient numbers and longer follow-up are required.

9 Discussion

Laparoscopic adrenalectomy has become the procedure of choice for most adrenal pathologies. Many case series have demonstrated the benefits in terms of blood loss, morbidity, analgesic requirements and hospital stay compared to the traditional open technique. However, a number uncertainties related to the laparoscopic procedure remain.

The thesis aimed to look at some of these uncertainties. As stated in Chapter 2 the aims were:

1. To document the surgical importance of variable vein anatomy and multiple periadrenal vessels during laparoscopic adrenalectomy.

2. To review the importance of the adrenal gland blood supply when performing a laparoscopic subtotal adrenalectomy.

3. To look at the perioperative haemodynamic changes in patients undergoing laparoscopic adrenalectomy for phaeochromocytomas and other adrenal tumours.

4. To assess the role of laparoscopic adrenalectomy for adrenal tumours of 6cm or greater.

5. To assess the outcomes of open adrenalectomy in a consecutive series of patients referred with adrenal tumours.

6. To assess the role of laparoscopic adrenalectomy for patients with isolated adrenal metastasis.

Chapters 3 and 4 examined different aspects of adrenal gland vasculature.

Chapter 3 examined the surgical importance of variable vein anatomy and multiple periadrenal vessels during LA. The study showed, with the magnified view (2.5-3 times normal) at laparoscopy, the main adrenal venous drainage (and any variants) could be clearly defined for all patients. The majority of patients (97%) had constant venous drainage. No bleeding complications or conversions resulted from failure to recognise the main adrenal vein and its variants. Other multiple, small periadrenal vessels were noted at time of laparoscopy for all patients. It was not possible to distinguish between small veins and arteries. These periadrenal

vessels were all small enough to be controlled with electrocautery or ultrasonic dissection. Adrenal vein variants and an increased number of periadrenal vessels appeared to occur in patients with phaeochromocytomas or large adrenocortical carcinomas. Increased attention to the adrenal gland vasculature may be required during LA for these patients.

After showing the constant nature of the main adrenal veins for patients undergoing LA, the next aim was to examine the nature of the periadrenal vessels. This would be important when performing laparoscopic subtotal adrenalectomy as a satisfactory blood supply of the adrenal remnant is vital to preserve steroid function.

Chapter 4 examined the importance of the adrenal gland blood supply when performing a laparoscopic subtotal adrenalectomy. This study has shown from cadaver dissection multiple small arteries and veins (in addition to the main adrenal vein) completely surround the adrenal gland. Using gross dissection and histological methods we demonstrated it was possible to follow the venous drainage from the adrenal gland to the peripheral veins. This has helped establish that these peripheral veins drain the adrenal gland. Therefore, during laparoscopic subtotal adrenalectomy, a non functioning adrenal remnant would be unlikely due to an inadequate arterial supply or due to division of the main adrenal vein. However, once the main adrenal vein is divided, excessive mobilisation of the adrenal remnant should be avoided to prevent destruction of the smaller peripheral veins necessary for venous drainage.

Perioperative haemodynamic changes are well recognised sequelae of adrenalectomy for phaeochromccytomas. In the current series, we used a phenoxybenzamine regimen and felt complete alpha blockade was achieved in all cases. As a result, we felt using this regimen and a specialist endocrine, anaesthetic and surgical team the perioperative haemodynamic stability

of LA for phaeochromocytoma has improved to such a degree that they may now be comparable to LA for other non-catecholamine secreting adrenal tumours.

Chapter 5 compared the perioperative haemodynamic changes in consecutive patients undergoing LA for phaeochromocytomas and other adrenal tumours. This study showed laparoscopic adrenalectomy for phaeochromocytoma was associated with increased episodes of severe intraoperative hypertension (systolic blood pressure=200-220mmHg) when compared to the laparoscopic resection of other adrenal tumours. These episodes were all controlled with anti-hypertensive medication. There were no other significant differences in terms of hypotensive episodes, cardiac arrhythmias or intravenous fluid requirements. This has demonstrated, in the presence of an experienced multidisciplinary team and complete preoperative alpha blockade, laparoscopic adrenalectomy for phaeochromocytoma can be accomplished with low perioperative haemodynamic complications.

It is uncertain if the laparoscopic resection of large (≥6cm) potentially malignant adrenal tumours is appropriate due to concerns over incomplete resection and local recurrence.

Chapter 6 compared the outcomes of LA for tumours ≥6cm with those <6cm. In the absence of local invasion, this study has shown the oncological outcome and post-operative morbidity of laparoscopic adrenalectomy for patients with tumours ≥6cm was comparable to those with tumours <6cm. Post-operative stay was a day longer (3 rather than 2 days). Concern over incomplete resection and local recurrence for these large adrenal tumours has not been realised. This has helped confirm a policy of initial laparoscopic resection for all non-invasive adrenal tumours can be applied safely. This would prevent patients undergoing unnecessary open procedures and allow the benefits of laparoscopy.

Chapter 7 examined the outcomes of open adrenalectomy in a consecutive series of patients referred with adrenal tumours. We showed, in the laparoscopic adrenalectomy era, OA was

required infrequently. In the absence of the requirement for an additional open procedure, OA was a demanding procedure associated with resection of adjacent structures and high local recurrence rates.

Chapter 8 examined the outcomes of laparoscopic adrenalectomy for patients with isolated adrenal metastasis. In the current series, the recovery and oncological outcomes for isolated adrenal metastasis from a renal origin compared very favourably to other series where a more selective policy for laparoscopy was adopted.

There were a number of limitations in this study. The main observations from chapters 3-8 were based on a retrospective review of a case series (Level 4 evidence). Limitations from this type of study include: selection bias, incomplete or inaccurate data. However, from the present series, patients referred for adrenalectomy were reviewed by a single surgeon (PJOD) and entered on to a prospective database. Adrenalectomy was then performed by the same surgeon. This would enable totality of practice to be documented and reduce the risk of incomplete data.

Ideally, from the present study, randomized controlled trials should be performed to confirm the observations. However, there are a number of reasons it seems unlikely these would be performed. Due to the rarity of adrenal tumours, it would not be possible to recruit a large enough number of patients to establish the studied outcomes. Another reason includes an existing body of evidence from case series giving overall consistent results. For example, chapter 6 documented the favourable postoperative and oncological outcomes of adrenalectomy for large noninvasive tumours (≥6cm). It was difficult to compare to other LA series for large tumours due to a number of limitations, including selection criteria and a low number of patients with large adrenal tumours. Despite this, the results of our series were consistent with the other retrospective case series. Therefore, despite the lack of strong

scientific evidence, it seems randomised prospective studies will not be performed and LA for large adrenal tumours has become an accepted procedure within experienced units.

Chapter 5 was a retrospective study comparing the perioperative haemodynamic changes in consecutive patients undergoing LA for phaeochromocytomas and other adrenal tumours. Specific limitations to this chapter include the accuracy or completeness of pulse and blood pressure measurements manually recorded on to the anaesthetic charts. We used definitions of tachycardia, hypertension, hypotension and length of an event to try and reduce the chance of missing any major haemodynamic complications.

Further Work

It would be useful to know the rate of incisional hernia formation after long term follow-up following laparoscopic adrenalectomy. There are plans to examine this from the current cohort of patients.

Also it would be important to further examine the role of the hand port for the laparoscopic resection of large adrenal masses >10cm.

References

Anson, B. J., & Caudwell, E. W. (1948). The anatomy of the para-renal system of veins, with comments on the renal arteries. *Journal of Urology, 60*(5), 714-737.

Assalia, A., & Gagner, M. (2004). Laparoscopic adrenalectomy. *British Journal of Surgery, 91*(10), 1259-1274.

Aubert, S., Wacrenier, A., Leroy, X., Devos, P., Carnaille, B., Proye, C., et al. (2002). Weiss system revisited: A clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. *American Journal of Surgical Pathology, 26*(12), 1612-1619.

Bauters, C., Vantyghem, M. C., Leteurtre, E., Odou, M. F., Mouton, C., Porchet, N., et al. (2003). Hereditary phaeochromocytomas and paragangliomas: A study of five susceptibility genes. *Journal of Medical Genetics, 40*(6), e75.

Bellantone, R., Ferrante, A., Boscherini, M., Lombardi, C. P., Crucitti, P., Crucitti, F., et al. (1997). Role of reoperation in recurrence of adrenal cortical carcinoma: Results from 188 cases collected in the italian national registry for adrenal cortical carcinoma. *Surgery, 122*(6), 1212-1218.

Boland, G. W., Blake, M. A., Hahn, P. F., & Mayo-Smith, W. W. (2008). Incidental adrenal lesions: Principles, techniques, and algorithms for imaging characterization. *Radiology, 249*(3), 756-775.

Boland, G. W., Lee, M. J., Gazelle, G. S., Halpern, E. F., McNicholas, M. M., & Mueller, P. R. (1998). Characterization of adrenal masses using unenhanced CT: An analysis of the CT literature. *AJR.American Journal of Roentgenology, 171*(1), 201-204.

Bonjer, H. J., Sorm, V., Berends, F. J., Kazemier, G., Steyerberg, E. W., de Herder, W. W., et al. (2000). Endoscopic retroperitoneal adrenalectomy: Lessons learned from 111 consecutive cases. *Annals of Surgery, 232*(6), 796-803.

Bonnet, S., Gaujoux, S., Leconte, M., Thillois, J. M., Tissier, F., & Dousset, B. (2008). Laparoscopic adrenalectomy for metachronous metastasis from renal cell carcinoma. *World Journal of Surgery, 32*(8), 1809-1814.

Bovio, S., Cataldi, A., Reimondo, G., Sperone, P., Novello, S., Berruti, A., et al. (2006). Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. *Journal of Endocrinological Investigation, 29*(4), 298-302.

Brauckhoff, M., Gimm, O., Thanh, P. N., Bar, A., Ukkat, J., Brauckhoff, K., et al. (2003). Critical size of residual adrenal tissue and recovery from impaired early postoperative adrenocortical function after subtotal bilateral adrenalectomy. *Surgery, 134*(6), 1020-1027.

Brauckhoff, M., Stock, K., Stock, S., Lorenz, K., Sekulla, C., Brauckhoff, K., et al. (2008). Limitations of intraoperative adrenal remnant volume measurement in patients undergoing subtotal adrenalectomy. *World Journal of Surgery, 32*(5), 863-872.

Brauckhoff, M., Thanh, P. N., Gimm, O., Bar, A., Brauckhoff, K., & Dralle, H. (2003). Functional results after endoscopic subtotal cortical-sparing adrenalectomy. *Surgery Today, 33*(5), 342-348.

Bravo, E. L., & Tagle, R. (2003). Pheochromocytoma: State-of-the-art and future prospects. *Endocrine Reviews, 24*(4), 539-553.

Brunt, L. M., Doherty, G. M., Norton, J. A., Soper, N. J., Quasebarth, M. A., & Moley, J. F. (1996). Laparoscopic adrenalectomy compared to open adrenalectomy for benign adrenal neoplasms. *Journal of the American College of Surgeons, 183*(1), 1-10.

Cheah, W. K., Clark, O. H., Horn, J. K., Siperstein, A. E., & Duh, Q. Y. (2002). Laparoscopic adrenalectomy for pheochromocytoma. *World Journal of Surgery, 26*(8), 1048-1051.

Clark, K. (1959). The blood vessels of the adrenal gland. *Journal of the Royal College of Surgeons of Edinburgh, 4*(3), 257-262.

Dackiw, A. P., Lee, J. E., Gagel, R. F., & Evans, D. B. (2001). Adrenal cortical carcinoma. *World Journal of Surgery, 25*(7), 914-926.

Dudley, N. E., & Harrison, B. J. (1999). Comparison of open posterior versus transperitoneal laparoscopic adrenalectomy. *British Journal of Surgery, 86*(5), 656-660.

Duh, Q. Y. (2002). Adrenal incidentalomas. *British Journal of Surgery, 89*(11), 1347-1349.

Eldeiry, L. S., & Garber, J. R. (2008). Adrenal incidentalomas, 2003 to 2005: Experience after publication of the national institutes of health consensus statement. *Endocrine Practice, 14*(3), 279-284.

El-Sherief, M. A. (1982). Adrenal vein catheterization. anatomic considerations. *Acta Radiologica: Diagnosis, 23*(4), 345-360.

Fernandez-Cruz, L., Taura, P., Saenz, A., Benarroch, G., & Sabater, L. (1996). Laparoscopic approach to pheochromocytoma: Hemodynamic changes and catecholamine secretion. *World Journal of Surgery, 20*(7), 762-768.

Gagner, M., Lacroix, A., & Bolt, E. (1992). Laparoscopic adrenalectomy in cushing's syndrome and pheochromocytoma. *New England Journal of Medicine, the, 327*(14), 1033-1033.

Gagner, M., Pomp, A., Heniford, B. T., Pharand, D., & Lacroix, A. (1997). Laparoscopic adrenalectomy: Lessons learned from 100 consecutive procedures. *Annals of Surgery, 226*(3), 238-246.

Gicquel, C., Baudin, E., Lebouc, Y., & Schlumberger, M. (1997). Adrenocortical carcinoma. *Annals of Oncology, 8*(5), 423-427.

Gotoh, M., Ono, Y., Hattori, R., Kinukawa, T., & Ohshima, S. (2002). Laparoscopic adrenalectomy for pheochromocytoma: Morbidity compared with adrenalectomy for tumors of other pathology. *Journal of Endourology, 16*(4), 245-249.

Gray, H., & Williams, P. L. (1989). *Gray's anatomy* (37th ed.). Edinburgh: Churchill Livingstone.

Hanssen, W. E., Kuhry, E., Casseres, Y. A., de Herder, W. W., Steyerberg, E. W., & Bonjer, H. J. (2006). Safety and efficacy of endoscopic retroperitoneal adrenalectomy. *British Journal of Surgery, 93*(6), 715-719.

Hardy, R., & Lennard, T. W. (2008). Subtotal adrenalectomy. *British Journal of Surgery, 95*(9), 1075-1076.

Hazzan, D., Shiloni, E., Golijanin, D., Jurim, O., Gross, D., & Reissman, P. (2001). Laparoscopic vs open adrenalectomy for benign adrenal neoplasm. *Surgical Endoscopy, 15*(11), 1356-1358.

Henry, J. F., Sebag, F., Iacobone, M., & Mirallie, E. (2002). Results of laparoscopic

　　adrenalectomy for large and potentially malignant tumors. *World Journal of Surgery,*

　　26(8), 1043-1047.

Ikeda, Y., Takami, H., Niimi, M., Kan, S., Sasaki, Y., & Takayama, J. (2001). Laparoscopic

　　partial or cortical-sparing adrenalectomy by dividing the adrenal central vein. *Surgical*

　　Endoscopy, 15(7), 747-750.

Imai, T., Kikumori, T., Ohiwa, M., Mase, T., & Funahashi, H. (1999). A case-controlled study of

　　laparoscopic compared with open lateral adrenalectomy. *American Journal of Surgery,*

　　178(1), 50-53.

Imai, T., Tanaka, Y., Kikumori, T., Ohiwa, M., Matsuura, N., Mase, T., et al. (1999).

　　Laparoscopic partial adrenalectomy. *Surgical Endoscopy, 13*(4), 343-345.

Inabnet, W. B., Pitre, J., Bernard, D., & Chapuis, Y. (2000). Comparison of the hemodynamic

　　parameters of open and laparoscopic adrenalectomy for pheochromocytoma. *World*

　　Journal of Surgery, 24(5), 574-578.

Jacobs, J. K., Goldstein, R. E., & Geer, R. J. (1997). Laparoscopic adrenalectomy. A new

　　standard of care. *Annals of Surgery, 225*(5), 495-501.

Janetschek, G., Finkenstedt, G., Gasser, R., Waibel, U. G., Peschel, R., Bartsch, G., et al.

　　(1998). Laparoscopic surgery for pheochromocytoma: Adrenalectomy, partial resection,

　　excision of paragangliomas. *Journal of Urology, 160*(2), 330-334.

Johnstone, F. R. (1957). The suprarenal veins. *American Journal of Surgery, 94*(4), 615-620.

Joris, J. L., Hamoir, E. E., Hartstein, G. M., Meurisse, M. R., Hubert, B. M., Charlier, C. J., et al. (1999). Hemodynamic changes and catecholamine release during laparoscopic adrenalectomy for pheochromocytoma. *Anesthesia & Analgesia, 88*(1), 16-21.

Kercher, K. W., Park, A., Matthews, B. D., Rolband, G., Sing, R. F., & Heniford, B. T. (2002). Laparoscopic adrenalectomy for pheochromocytoma. *Surgical Endoscopy, 16*(1), 100-102.

Kim, S. H., Brennan, M. F., Russo, P., Burt, M. E., & Coit, D. G. (1998a). The role of surgery in the treatment of clinically isolated adrenal metastasis. *Cancer, 82*(2), 389-394.

Kim, S. H., Brennan, M. F., Russo, P., Burt, M. E., & Coit, D. G. (1998b). The role of surgery in the treatment of clinically isolated adrenal metastasis. *Cancer, 82*(2), 389-394.

Kinney, M. A., Warner, M. E., vanHeerden, J. A., Horlocker, T. T., Young, W. F.,Jr, Schroeder, D. R., et al. (2000). Perianesthetic risks and outcomes of pheochromocytoma and paraganglioma resection. *Anesthesia & Analgesia, 91*(5), 1118-1123.

Kloos, R. T., Gross, M. D., Francis, I. R., Korobkin, M., & Shapiro, B. (1995). Incidentally discovered adrenal masses. *Endocrine Reviews, 16*(4), 460-484.

Kok, K. Y., & Yapp, S. K. (2002). Laparoscopic adrenal-sparing surgery for primary hyperaldosteronism due to aldosterone-producing adenoma. *Surgical Endoscopy, 16*(1), 108-111.

Korobkin, M., Giordano, T. J., Brodeur, F. J., Francis, I. R., Siegelman, E. S., Quint, L. E., et al. (1996). Adrenal adenomas: Relationship between histologic lipid and CT and MR findings. *Radiology, 200*(3), 743-747.

Lebuffe, G., Dosseh, E. D., Tek, G., Tytgat, H., Moreno, S., Tavernier, B., et al. (2005). The

effect of calcium channel blockers on outcome following the surgical treatment of

phaeochromocytomas and paragangliomas. *Anaesthesia, 60*(5), 439-444.

Lee, J. E., Evans, D. B., Hickey, R. C., Sherman, S. I., Gagel, R. F., Abbruzzese, M. C., et al.

(1998). Unknown primary cancer presenting as an adrenal mass: Frequency and

implications for diagnostic evaluation of adrenal incidentalomas. *Surgery, 124*(6), 1115-

1122.

Linnoila, R. I., Keiser, H. R., Steinberg, S. M., & Lack, E. E. (1990). Histopathology of benign

versus malignant sympathoadrenal paragangliomas: Clinicopathologic study of 120 cases

including unusual histologic features. *Human Pathology, 21*(11), 1168-1180.

Linos, D. A., Stylopoulos, N., Boukis, M., Souvatzoglou, A., Raptis, S., & Papadimitriou, J.

(1997). Anterior, posterior, or laparoscopic approach for the management of adrenal

diseases?. *American Journal of Surgery, 173*(2), 120-125.

Luketich, J. D., & Burt, M. E. (1996). Does resection of adrenal metastases from non-small cell

lung cancer improve survival?. *Annals of Thoracic Surgery, 62*(6), 1614-1616.

MacGillivray, D. C., Shichman, S. J., Ferrer, F. A., & Malchoff, C. D. (1996). A comparison of

open vs laparoscopic adrenalectomy. *Surgical Endoscopy, 10*(10), 987-990.

MacGillivray, D. C., Whalen, G. F., Malchoff, C. D., Oppenheim, D. S., & Shichman, S. J.

(2002). Laparoscopic resection of large adrenal tumors. *Annals of Surgical Oncology,

9*(5), 480-485.

Mercan, S., Seven, R., Ozarmagan, S., & Tezelman, S. (1995). Endoscopic retroperitoneal

adrenalectomy. *Surgery, 118*(6), 1071-1075.

Mikaelsson, C. G. (1970). Venous communications of the adrenal glands. anatomic and circulatory studies. *Acta Radiologica: Diagnosis, 10*(5), 369-393.

Monkhouse, W. S., & Khalique, A. (1986). The adrenal and renal veins of man and their connections with azygos and lumbar veins. *Journal of Anatomy, 146*, 105-115.

Ortega, J., Sala, C., Garcia, S., & Lledo, S. (2002). Cost-effectiveness of laparoscopic vs open adrenalectomy: Small savings in an expensive process. *Journal of Laparoendoscopic & Advanced Surgical Techniques.Part A, 12*(1), 1-5.

Palazzo, F. F., Sebag, F., Sierra, M., Ippolito, G., Souteyrand, P., & Henry, J. F. (2006). Long-term outcome following laparoscopic adrenalectomy for large solid adrenal cortex tumors. *World Journal of Surgery, 30*(5), 893-898.

Park, B. K., Kim, C. K., Kim, B., & Lee, J. H. (2007). Comparison of delayed enhanced CT and chemical shift MR for evaluating hyperattenuating incidental adrenal masses. *Radiology, 243*(3), 760-765.

Paul, C. A., Virgo, K. S., Wade, T. P., Audisio, R. A., & Johnson, F. E. (2000). Adrenalectomy for isolated adrenal metastases from non-adrenal cancer. *International Journal of Oncology, 17*(1), 181-187.

Petri, B. J., van Eijck, C. H., de Herder, W. W., Wagner, A., & de Krijger, R. R. (2009). Phaeochromocytomas and sympathetic paragangliomas. *British Journal of Surgery, 96*(12), 1381-1392.

Pisanu, A., Jafari, M., Pattou, F., Carnaille, B., & Proye, C. (2001). Indications for adrenalectomy in the laparoscopic era. *Giornale Di Chirurgia, 22*(3), 101-106.

Plouin, P. F., Duclos, J. M., Soppelsa, F., Boublil, G., & Chatellier, G. (2001). Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: Analysis of 165 operations at a single center. *Journal of Clinical Endocrinology & Metabolism, 86*(4), 1480-1486.

Proye, C., Thevenin, D., Cecat, P., Petillot, P., Carnaille, B., Verin, P., et al. (1989). Exclusive use of calcium channel blockers in preoperative and intraoperative control of pheochromocytomas: Hemodynamics and free catecholamine assays in ten consecutive patients. *Surgery, 106*(6), 1149-1154.

Prys-Roberts, C. (2000). Phaeochromocytoma--recent progress in its management. *British Journal of Anaesthesia, 85*(1), 44-57.

Prys-Roberts, C., & Farndon, J. R. (2002). Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World Journal of Surgery, 26*(8), 1037-1042.

Ramacciato, G., Mercantini, P., La Torre, M., Di Benedetto, F., Ercolani, G., Ravaioli, M., et al. (2008). Is laparoscopic adrenalectomy safe and effective for adrenal masses larger than 7 cm?. *Surgical Endoscopy, 22*(2), 516-521.

Rayan, S. S., & Hodin, R. A. (2000). Short-stay laparoscopic adrenalectomy. *Surgical Endoscopy, 14*(6), 568-572.

Ross, E. J., Prichard, B. N., Kaufman, L., Robertson, A. I., & Harries, B. J. (1967). Preoperative and operative management of patients with phaeochromocytoma. *British Medical Journal, 1*(5534), 191-198.

Roukounakis, N., Dimas, S., Kafetzis, I., Bethanis, S., Gatsulis, N., Kostas, H., et al. (2007). Is preservation of the adrenal vein mandatory in laparoscopic adrenal-sparing surgery?. *Journal of the Society of Laparoendoscopic Surgeons, 11*(2), 215-218.

Sarela, A. I., Murphy, I., Coit, D. G., & Conlon, K. C. (2003). Metastasis to the adrenal gland: The emerging role of laparoscopic surgery. *Annals of Surgical Oncology, 10*(10), 1191-1196.

Sasano, H., Shizawa, S., & Nagura, H. (1995). Adrenocortical cytopathology. *American Journal of Clinical Pathology, 104*(2), 161-166.

Saunders, B. D., Wainess, R. M., Dimick, J. B., Upchurch, G. R., Doherty, G. M., & Gauger, P. G. (2004). Trends in utilization of adrenalectomy in the united states: Have indications changed?. *World Journal of Surgery, 28*(11), 1169-1175.

Schell, S. R., Talamini, M. A., & Udelsman, R. (1999). Laparoscopic adrenalectomy for nonmalignant disease: Improved safety, morbidity, and cost-effectiveness. *Surgical Endoscopy, 13*(1), 30-34.

Sebag, F., Calzolari, F., Harding, J., Sierra, M., Palazzo, F. F., & Henry, J. F. (2006). Isolated adrenal metastasis: The role of laparoscopic surgery. *World Journal of Surgery, 30*(5), 888-892.

Shen, W. T., Kebebew, E., Clark, O. H., & Duh, Q. Y. (2004). Reasons for conversion from laparoscopic to open or hand-assisted adrenalectomy: Review of 261 laparoscopic adrenalectomies from 1993 to 2003. *World Journal of Surgery, 28*(11), 1176-1179.

Shen, W. T., Lim, R. C., Siperstein, A. E., Clark, O. H., Schecter, W. P., Hunt, T. K., et al. (1999). Laparoscopic vs open adrenalectomy for the treatment of primary hyperaldosteronism. *Archives of Surgery, 134*(6), 628-631.

Sinnatamby, C. S., & Last, R. J. (1999). *Last's anatomy : Regional and applied* (10th ed.). Edinburgh: Churchill Livingstone.

Soares, R. L.,Jr, Monchik, J., Migliori, S. J., & Amaral, J. F. (1999). Laparoscopic adrenalectomy for benign adrenal neoplasms. *Surgical Endoscopy, 13*(1), 40-42.

Song, J. H., Chaudhry, F. S., & Mayo-Smith, W. W. (2007). The incidental indeterminate adrenal mass on CT (> 10 H) in patients without cancer: Is further imaging necessary? follow-up of 321 consecutive indeterminate adrenal masses. *AJR.American Journal of Roentgenology, 189*(5), 1119-1123.

Soon, P. S., Yeh, M. W., Delbridge, L. W., Bambach, C. P., Sywak, M. S., Robinson, B. G., et al. (2008). Laparoscopic surgery is safe for large adrenal lesions. *European Journal of Surgical Oncology, 34*(1), 67-70.

Sprung, J., O'Hara, J. F.,Jr, Gill, I. S., Abdelmalak, B., Sarnaik, A., & Bravo, E. L. (2000). Anesthetic aspects of laparoscopic and open adrenalectomy for pheochromocytoma. *Urology, 55*(3), 339-343.

Staren, E. D., & Prinz, R. A. (1996). Adrenalectomy in the era of laparoscopy. *Surgery, 120*(4), 706-709.

Strong, V. E., D'Angelica, M., Tang, L., Prete, F., Gonen, M., Coit, D., et al. (2007). Laparoscopic adrenalectomy for isolated adrenal metastasis. *Annals of Surgical Oncology, 14*(12), 3392-3400.

Sturgeon, C., Shen, W. T., Clark, O. H., Duh, Q. Y., & Kebebew, E. (2006). Risk assessment in 457 adrenal cortical carcinomas: How much does tumor size predict the likelihood of malignancy?. *Journal of the American College of Surgeons, 202*(3), 423-430.

Tauzin-Fin, P., Sesay, M., Gosse, P., & Ballanger, P. (2004). Effects of perioperative alpha1 block on haemodynamic control during laparoscopic surgery for phaeochromocytoma. *British Journal of Anaesthesia, 92*(4), 512-517.

Thompson, G. B., Grant, C. S., van Heerden, J. A., Schlinkert, R. T., Young, W. F.,Jr, Farley, D. R., et al. (1997). Laparoscopic versus open posterior adrenalectomy: A case-control study of 100 patients. *Surgery, 122*(6), 1132-1136.

Thompson, G. B., & Young, W. F.,Jr. (2003). Adrenal incidentaloma. *Current Opinion in Oncology, 15*(1), 84-90.

Thompson, L. D. (2002). Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms: A clinicopathologic and immunophenotypic study of 100 cases. *American Journal of Surgical Pathology, 26*(5), 551-566.

Ting, A. C., Lo, C. Y., & Lo, C. M. (1998). Posterior or laparoscopic approach for adrenalectomy. *American Journal of Surgery, 175*(6), 488-490.

Valeri, A., Borrelli, A., Presenti, L., Lucchese, M., Venneri, F., Mannelli, M., et al. (2001). Adrenal masses in neoplastic patients: The role of laparoscopic procedure. *Surgical Endoscopy, 15*(1), 90-93.

van der Harst, E., Bruining, H. A., Jaap Bonjer, H., van der Ham, F., Dinjens, W. N., Lamberts, S. W., et al. (2000). Proliferative index in phaeochromocytomas: Does it predict the occurrence of metastases?. *Journal of Pathology, 191*(2), 175-180.

Vargas, H. I., Kavoussi, L. R., Bartlett, D. L., Wagner, J. R., Venzon, D. J., Fraker, D. L., et al. (1997). Laparoscopic adrenalectomy: A new standard of care. *Urology, 49*(5), 673-678.

Vassilopoulou-Sellin, R., & Schultz, P. N. (2001). Adrenocortical carcinoma. clinical outcome at the end of the 20th century. *Cancer, 92*(5), 1113-1121.

Walz, M. K., Alesina, P. F., Wenger, F. A., Deligiannis, A., Szuczik, E., Petersenn, S., et al. (2006). Posterior retroperitoneoscopic adrenalectomy--results of 560 procedures in 520 patients. *Surgery, 140*(6), 943-948.

Walz, M. K., Peitgen, K., Saller, B., Giebler, R. M., Lederbogen, S., Nimtz, K., et al. (1998). Subtotal adrenalectomy by the posterior retroperitoneoscopic approach. *World Journal of Surgery, 22*(6), 621-626.

Walz, M. K., Petersenn, S., Koch, J. A., Mann, K., Neumann, H. P., & Schmid, K. W. (2005). Endoscopic treatment of large primary adrenal tumours. *British Journal of Surgery, 92*(6), 719-723.

Weismann, D., Fassnacht, M., Weinberger, F., Hamelmann, W., Diehl, S., Lorenz, K., et al. (2006). Intraoperative haemodynamic stability in patients with phaeochromocytoma--minimally invasive vs conventional open surgery. *Clinical Endocrinology, 65*(3), 352-358.

Weiss, L. M. (1984). Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *American Journal of Surgical Pathology, 8*(3), 163-169.

Werbel, S. S., & Ober, K. P. (1995). Pheochromocytoma. update on diagnosis, localization, and management. *Medical Clinics of North America, 79*(1), 131-153.

Winfield, H. N., Hamilton, B. D., Bravo, E. L., & Novick, A. C. (1998). Laparoscopic

adrenalectomy: The preferred choice? A comparison to open adrenalectomy. *Journal of*

Urology, 160(2), 325-329.

Young, W. F.,Jr. (2000). Management approaches to adrenal incidentalomas. A view from

rochester, minnesota. *Endocrinology & Metabolism Clinics of North America, 29*(1), 159-

185.

Young, W. F.,Jr. (2007). Clinical practice. the incidentally discovered adrenal mass. *New*

England Journal of Medicine, 356(6), 601-610.

11 Presentations and published papers resulting from the present work

Presentations

CN Parnaby, PJ O'Dwyer. 'The role of laparoscopic adrenalectomy for adrenal tumours of 10cm or larger'. Oral presentation, International Surgical Congress, ASGBI, April 2010.

CN Parnaby, N Galbraith, PJ O'Dwyer. 'Patient outcome following laparoscopic adrenalectomy for adrenal metastasis.' Poster presentation, International Surgical Congress, ASGBI, April 2010.

CN Parnaby, P.S. Chong, L. Chisholm, J. Farrow, J.M. Connell, P.J. O' Dwyer. 'Laparoscopic adrenalectomy for potentially malignant tumours.' Oral presentation, International Surgical Congress, ASGBI, May 2008.

CN Parnaby, MG Serpell, JM Connell, PJ O' Dwyer. 'Perioperative haemodynamic changes in patients undergoing laparoscopic adrenalectomy for phaeochromocytomas and other adrenal tumours.' Poster presentation, International Surgical Congress, ASGBI, May 2008.

CN Parnaby, N Galbraith, PJ O'Dwyer. 'Importance of adrenal vein anatomy during laparoscopic adrenalectomy.' Oral presentation, British Association of Clinical Anatomists, December 2007.

CN Parnaby, PS Chong, MG Serpell, JM Connell, PJ O'Dwyer. 'Patients undergoing laparoscopic phaeochromocytoma resection do not require routine postoperative admission to the intensive care unit.' Poster presentation, European Association of Endoscopic Surgeons, Athens, July 2007.

CN Parnaby, P.S. Chong, L Chisholm, J Farrow, JM Connell, PJ O' Dwyer. 'The role of laparoscopic adrenalectomy in a consecutive series of patients with adrenal tumours.' Poster presentation, European Association of Endoscopic Surgeons, Athens, July 2007.

Publications

CN Parnaby, N Galbraith, PJ O'Dwyer. Importance of the adrenal gland blood supply during laparoscopic subtotal adrenalectomy. J Laparoendosc Adv Surg Tech A 2010; 20:311-5.

CN Parnaby, MG Serpell, JM Connell, PJ O'Dwyer. Perioperative haemodynamic changes in patients undergoing laparoscopic adrenalectomy for phaeochromocytomas and other adrenal tumours. The Surgeon 2010;8:9-14.

CN Parnaby, N Galbraith, PJ O'Dwyer. Experience in identifying the venous drainage of the adrenal gland during laparoscopic adrenalectomy. Clinical Anatomy 2008;21:660-665.

CN Parnaby, PS Chong, L Chisholm, J Farrow, JM Connell, PJ O' Dwyer.

The role of laparoscopic adrenalectomy for adrenal tumours of 6cm or greater. Surg Endosc 2008;22:617-621.