ONCOLOGY/RECONSTRUCTION
REVIEW

Adrenal masses: A urological perspective

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Abstract Adrenal masses have become increasingly common due to widespread use of sectional imaging. Urologists are commonly faced with management decisions in patients with adrenal masses. Systemic review of available literature related to surgical adrenal disease was performed to summarise the most pertinent information related to adrenal masses, diagnostic evaluation and surgical treatment. Detailed hormonal evaluation of adrenal disease was not included, being part of endocrinological rather than urological practice. Adrenal masses exhibit a wide spectrum of presentation and pathology, and treatment requires different surgical techniques. Full understanding of the pathology and management of such masses should be completely familiar to practicing urologists.

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Introduction

The adrenals are paired glands lying in the upper retroperitoneum superior and medial to the kidneys. The adrenal glands secrete a number of hormones that are critical for a wide variety of physiological functions. The outer portion or the adrenal cortex secretes

aldosterone, cortisol, and sex hormones, whilst the inner portion or the medulla is part of the sympathetic nervous system secreting catecholamines. With this varied range of physiological activity, functioning adrenal tumours can cause a wide spectrum of syndromes including hyperaldosteronism, Cushing's syndrome (cortisol excess), sympathetic overactivity, and less commonly virilisation or feminisation. Primary adrenal malignancy is rare but almost uniformly aggressive, whilst secondary metastatic tumours of the adrenal are common in a wide range of cancers.

Patients with adrenal masses are occasionally encountered by, or referred to urologists for evaluation and management. Because adrenal disease is not very common, and the spectrum of adrenal disease is wide, urologists often feel inexperienced when managing such patients. In the USA, urologists and general/endocrinological surgeons perform surgical treatment of adrenal disease equally. The urologist is better equipped to operate on the adrenal given the experience with retroperitoneal surgery and the difficult location of the adrenal glands. However, neither surgical specialty has the ability to completely evaluate patients functionally due to the extensive evaluation required, and wide symptom spectrum that may be present in patients with adrenal disease. Some of these conditions can be subtle and very difficult to diagnose. As such, a specialised endocrinologist is an essential part of the managing team for patients with adrenal disease in addition to the specialised surgeon or urologist. The present review aims to provide practicing urologists with the necessary information and framework for managing patients presenting with an adrenal mass.

Methods

A systematic search of published literature in the PubMed database between 1999 and 2015 was performed using the keywords 'adrenal mass', 'adrenal incidentaloma', 'adrenal imaging', and 'adrenal surgery'. Case reports and non-English literature were excluded. Occasional publications before the search window were included if considered to be important. No high level prospective randomised studies were found, with most of the literature consisting of retrospective series. An overview of topics and information considered to be important to the practicing urologist is presented. Detailed hormonal evaluation of adrenal masses is felt to be beyond the scope of the practicing urologist and was avoided, instead presenting a very brief screening for adrenal hyperfunction.

Adrenal incidentaloma

An adrenal incidentaloma is an adrenal mass that is >1 cm discovered incidentally on radiological evalua-

tion of a patient without signs or symptoms of adrenal disease or known malignancy. The prevalence of adrenal incidentaloma increases with age from <1% in patients younger than 30 years to ~7% in patients older than 70 years, and is bilateral in ~10% of cases [1]. In a more recent series using CT, the mean prevalence was 4% overall [2]. The incidence of different pathological types of lesions is summarised in Table 1. Although most adrenal incidentalomas are benign non-functional adenomas, additional functional and radiological evaluation is often indicated to exclude the less common asymptomatic functioning adrenal tumour or malignancy. The diagnostic approach in patients with adrenal incidentaloma is thus twofold: (i) to diagnose (or exclude) functioning adrenal tumour, and (ii) to diagnose (or exclude) primary or secondary malignancy.

Screening evaluating of adrenal masses

A complete history and careful physical examination should be carried out in any patient with an adrenal mass with careful attention to the manifestations of the different adrenal diseases, as well as to any history of malignancy. Whilst patients may occasionally present with symptoms of adrenal hyperfunction, screening for adrenal hyperfunction should also be carried out in all patients (including asymptomatic patients) to diagnose hormonally active adrenal masses. Such hyperfunction not only constitutes an indication for surgical excision, but in some cases also necessitates specific critical perioperative management to avoid patient morbidity. A detailed and complete adrenal hormonal evaluation is beyond the capability of most urologists and should be undertaken by a specialised endocrinologist, but the urologist, as detailed below, can easily undertake basic screening evaluation for the following entities:

- Phaeochromocytoma: 24-h urinary metanephrines (plasma metanephrines also acceptable).
- Hypercortisolism: 24-h urinary cortisol (or dexamethasone suppression test).
- Hyperaldosteronism: plasma aldosterone (compared to plasma renin – only indicated if patients are hypertensive, and/or hypokalaemia <3.5 mmol/L).

Table 1 Aetiology of adrenal incidentaloma.

Aetiology	%
Non-functioning cortical adenoma	70–80
Phaeochromocytoma	1–10
Adrenocortical carcinoma	<5
Subclinical Cushing's syndrome	5–20
Metastases	2.5
Primary aldosteronism	1–2
Others: myelolipoma, adrenal cyst, haemorrhage, schwannoma, infectious lesions (histoplasmosis, echinococcosis)	

- Androgens: serum   dehydroepiandrosterone,   17 ketosteroids.

Adrenal imaging

Adrenal adenomas have a high fat content because of sterol-rich tissue, and only about 20–30% of adrenal adenomas are fat poor. This high fat content forms the cornerstone of diagnostic imaging of the adrenals in differentiating benign from malignant lesions.

Adrenal CT

Adrenal CT is the current cornerstone of imaging of the adrenal glands. In addition to identifying the lesion, information obtained includes the density, size, calcification, necrosis, or local invasion. Unenhanced images are obtained first; enhanced images with i.v. contrast are used if additional information about contrast washout is needed. Adenomas being lipid rich, an adrenal lesion measuring less than 10 HU on non-contrast images (Fig. 1) is an adenoma in virtually 100% of cases regardless of size [3]. Lipid poor adenomas can measure between 10 and 20 HU, in these cases contrast scans are used and enhancement is measured at 60 s and 15 min. Absolute washout of contrast at 15 min > 60%, or relative washout (between 15 min and 1 min) > 40% is also diagnostic of an adenoma [4]. Unenhanced measurements > 30 HU usually denote phaeochromocytoma or adrenocortical carcinoma (Fig. 2). Further features suggestive of malignancy include large size, heterogeneous enhancement, necrosis,

Figure 1 1.8×1.3 cm right adrenal incidentaloma. Density measurements on unenhanced scan are 3 HU, consistent with a benign adenoma. No further radiological evaluation is indicated.

Figure 2   Heterogeneous enhancement in a patient with a right adrenal mass 1 min after i.v. contrast. Unenhanced images measured at 36 HU, at 15 min enhancement was 98 HU. CT findings highly suggestive of adrenocortical carcinoma, pathologically confirmed after adrenalectomy.

or invasion of adjacent organs. Macroscopic fat enhancement (< −40 HU) denotes myelolipoma of the adrenal gland.

Chemical shift MRI

In situations where the diagnosis is still unclear using CT, chemical shift T1-weighted MRI may be used. The lipid content of adenoma causes a drop in signal intensity during out-of-phase compared to in-phase images [5].

The risk of malignancy has traditionally relied upon the size of the adrenal lesion [6], with the incidence of malignancy of ~25% for tumours of > 6 cm, 1.2% for tumours of 4–6 cm, and 0% for lesions of < 4 cm in size. Another study showed the likelihood of cancer to be 10%, 19%, and 47% for tumours $\geqslant 4$ cm, $\geqslant 6$ cm, and $\geqslant 8$ cm, respectively [7]. With the added information obtained from adrenal CT or MRI, size alone does not constitute an indication for surgery if the lesion is accurately identified (e.g. adenoma, myelolipoma) on imaging studies.

Positron emission tomography (PET) scan

Fluorodeoxyglucose (FDG)-PET/CT is primarily useful in patients with known extra-adrenal malignancy. Adrenal nodules with standardised unit uptake (SUV) higher than the liver are likely to be malignant, whilst those with SUV units lower than the liver are likely to be benign. Adrenal PET/CT imaging has to take into

consideration the imaging characteristics of the primary malignancy, case in point for urologists is that most genitourinary malignancies do not show any increased uptake with PET/CT imaging, making the technique unreliable for imaging in the majority of the urological patient population.

Metaiodobenzylguanidine (MIBG) scan

MIBG is an analogue of noradrenaline and guanethidine that has selective uptake by chromaffin tissue cells in the adrenal (phaeochromocytoma) or extra-adrenal locations (paraganglionoma). Imaging is performed with the ^{123}I isotope due to shorter half-life and improved safety profile compared to the significantly longer half-life of ^{131}I. Although specific for phaeochromocytoma, the role of MIBG in diagnosis of the disease is secondary to laboratory testing and CT/MRI imaging. MIBG may be helpful in diagnosing and localising recurrent or metastatic phaeochromocytoma in difficult locations. Although quantitative analysis of MIBG uptake may suggest malignancy [8], definitive diagnosis of malignancy is ultimately determined by clinical behaviour of the tumour. High doses of the isotope ^{131}I MIBG is used as specific chromaffin tissue-targeted radiation therapy in patients with metastatic phaeochromocytoma.

Preoperative preparation in patients with functioning adrenal mass

Adequate perioperative management of patients with functioning adrenal masses is critical to decreasing patient morbidity during surgery. Apart from general preparation for surgery, patients with hyperfunctioning adrenal tumours require special considerations that are specific to the hormones being overproduced.

Patients with Cushing's syndrome require stress doses of steroids in the perioperative period, as cortisol production from the adrenal adenoma is autonomous and not responsive to the stress induced by surgery. Special care should be exercised during positioning as well as during surgery to avoid excessive bleeding, or skin or skeletal injury in these patients due to Cushing's induced osteoporosis, and skin and blood vessel fragility. Suppression of contralateral cortisol production necessitates postoperative cortisol replacement for a variable duration of time until the contralateral adrenal recovers function. After bilateral total adrenalectomy patients will require lifelong replacement of both cortico- and mineralosteroids. A specialised endocrinologist should undertake such detailed hormonal testing and replacement. It is important to remember that some patients with presumed non-functioning adrenal tumours may have subclinical Cushing's syndrome (SCS; see later) and present with adrenal insufficiency in the postoperative period after the presumed non-functioning adenoma is excised.

Patients with hypokalaemia from aldosterone overproduction require preoperative potassium replacement as well as treatment with potassium-sparing diuretics as needed to avoid cardiac arrhythmias related to hypokalaemia during surgery.

Preoperative preparation for patients with phaeochromocytoma requires pharmacological blockage to avoid extreme sympathetic overactivity during surgery that may be extremely dangerous to the patient. Several strategies to prepare patients have been used successfully. Most commonly an α-adrenergic blocker (like phenoxybenzamine) is started about 2 or 3 weeks before surgery to control blood pressure. In patients with significant tachycardia or other arrhythmias, a β-blocker is added after complete α blockade to control the heart rate and arrhythmia. An important consideration is that complete α blockade is essential before introduction of β-blockers; otherwise unopposed α-adrenergic activity would result in dangerously uncontrolled hypertension. Calcium channel blockers are another preoperative strategy that is adequate for preparing patients for surgery. All patients with phaeochromocytoma have a chronically contracted vascular space and require generous repletion of their intravascular volume preoperatively to prevent sudden or profound hypotension as the adrenergic stimulus is removed during surgery. This volume repletion is an essential part of preparing patients for surgery, in our institution the vast majority of patients are admitted preoperatively and generous hydration with normal saline overnight is used as the sole preoperative strategy for surgical preparation.

Surgery for patients with phaeochromocytoma can be a delicate endeavour for both surgeon and anaesthesiologist. On the surgical side, careful delicate dissection should be used to avoid undue pressure or squeezing of the tumour with resulting surges in catecholamine release. Early venous control is desirable but may not always be attainable, in a lot of cases the adrenal gland may have several venous channels draining the hormone production, and complete venous control is achieved only at the time of complete excision. The anaesthesiologist should be prepared to handle rapid increases in blood pressure and heart rate with the use of short acting i.v. medication (nitroprusside, esmolol), and should also be prepared to provide blood pressure support in case of hypotension after tumour excision. Prolonged hypotension and/or hypoglycaemia may occur for several days after surgery, requiring close monitoring of patients until they recover normal blood pressure and glycaemic parameters.

Subclinical Cushing's syndrome (SCS)

SCS is subtle autonomous production of cortisol from an adrenal mass, usually associated with suppression of cortisol production from the contralateral gland,

without overt clinical signs of Cushing's syndrome [9]. SCS has been linked to patient morbidity similar to Cushing's disease (hypertension, obesity, osteoporosis, etc.), and has been reported in up to 20% of patients with adrenal incidentaloma [10]. A small percentage (∼12%) of patients with SCS have been reported to progress to clinical Cushing's syndrome [11]. SCS is an important consideration to keep in mind during and after adrenalectomy on a patient with a suspected non-functional adrenal tumour, as these patients may develop postoperative adrenal insufficiency requiring steroid replacement therapy.

Adrenocortical carcinoma

Adrenocortical carcinoma is a rare but aggressive tumour of the adrenal with an incidence about 1 in a million. It is slightly more common in females. Most cases are sporadic, with a minority of cases occurring in patients with multiple endocrine neoplasia or Li-Fraumeni syndromes. Although a small percentage of small adrenocortical carcinomas may be discovered incidentally, more commonly large tumours present with pain, abdominal mass, or symptoms of metastatic disease. About 50–60% are hormonally active and present with symptoms of hormone excess, with Cushing's syndrome being most common, followed by a combination of Cushing's syndrome with virilisation, feminisation, hyperaldosteronism, and virilisation alone in order of frequency. Adequate hormonal evaluation is necessary in all cases to allow important perioperative management as well as postoperative hormonal replacement as needed. Radiological features suggestive of malignancy include large size, invasion of adjacent organs, necrosis, heterogeneous enhancement, and occasional presence of inferior vena cava thrombus (Fig. 3).

Tumour stage at diagnosis and completeness of surgical resection are the major determinants of patient survival [12]. Complete surgical resection with negative margins offers the only hope for cure in patients with localised disease. Adequate preoperative planning is essential with careful attention to hormone hypersecretion, as well as anatomical details that impact surgery, such as the possibility of adjacent organ involvement or the presence of venous thrombus. The presence of venous thrombus requires vascular control of the vena cava with the possibility of cardiopulmonary bypass for tumours extending above the diaphragm. The practice of routine ipsilateral nephrectomy with adrenalectomy for carcinoma has been challenged and is currently not indicated unless the kidney is directly involved with tumour or renal vein thrombus precludes sparing the kidney [13,14]. Regional lymphadenectomy is generally recommended and decreases the chances of tumour recurrence, as well as disease-specific mortality. Suggested boundaries include the crus of the diaphragm,

Figure 3 Left adrenocortical carcinoma with renal vein and inferior vena cava tumour thrombus reaching the right atrium. Additional radiological features of malignancy are large size and heterogeneous enhancement.

the ipsilateral great vessel and the ipsilateral renal hilum [15]. Open surgical adrenalectomy is generally associated with better patient outcome than minimally invasive adrenalectomy, unless for small tumours in experienced centres [16]. Adjuvant use of mitotane has been reported to result in improved disease-specific survival in patients after undergoing surgical resection [17], but poor tolerability is a major restricting factor to generalised drug use. A reasonable approach would be to offer adjuvant mitotane to patients with a high risk of recurrence after surgery (advanced stage, positive margins), and avoid adjuvant treatment in patients with lower risk of recurrence (early stage, complete resection) [18].

Surgical approaches to adrenalectomy

Indications for adrenalectomy are hormonally active tumour or suspected malignancy. Since the introduction of laparoscopic adrenalectomy by Gagner et al. [19] in 1990, minimally invasive techniques have become established as the primary surgical approach for benign adrenal disease. Adrenalectomy is perfectly suited to minimally invasive surgery because laparoscopy allows easy access to a relatively small gland located in a very high retroperitoneal location necessitating large muscle cutting incisions for open surgical access. Minimally invasive adrenal surgery has proliferated due to equivalent surgical outcomes but minimal blood loss, lower pain, improved cosmesis, and shorter recovery as compared to open surgery [20,21]. The disadvantage

of minimally invasive adrenalectomy is the need for additional laparoscopic equipment, the steep learning curve, and the inability to operate on large or locally invasive adrenal masses.

Laparoscopic adrenalectomy

The most commonly used technique is laparoscopic adrenalectomy, which has been described and widely used through both transperitoneal and retroperitoneal approaches. Neither approach is superior and both are performed by surgeons based on their individual surgical preferences. The retroperitoneal approach provides an advantage for patients with multiple previous abdominal surgeries when avoiding the peritoneal cavity is desirable [22]. The retroperitoneum can be accessed through the flank or the posterior directions, and the posterior approach may offer an advantage for obese patients. The technical details of each approach are beyond the scope of the present review.

Robotic and laparoendoscopic single-site (LESS) adrenalectomy

More recent evolutions to standard laparoscopic adrenalectomy include robot-assisted adrenalectomy as well as LESS adrenalectomy. Robotic assistance has been applied to a wide range of surgical procedures including adrenalectomy [23]. The advantage of adding robotic assistance for adrenalectomy is unclear in most cases, although it may provide added utility in cases of partial adrenalectomy where cortical sparing is important. The robotic approach has the disadvantage of increased expense and limited availability compared to standard laparoscopy. LESS adrenalectomy has also evolved concurrent with evolution of LESS for other surgical procedures, and has been successfully reported for adrenalectomy. Improved cosmesis is the main attraction; overall advantages remain unclear in view of the minimal instrumentation required for standard laparoscopic adrenalectomy and the significantly added difficulty and operative time needed for LESS approach [24].

Open surgical adrenalectomy

Open surgical adrenalectomy is indicated for known or suspected adrenocortical carcinoma with the exception of small lesions in experienced centres. Open surgical adrenalectomy offers the advantages of gentler handling of large tumours or phaeochromocytoma, and the ability to explore or resect adjacent organs in cases of local invasion [25]. The results of open surgical adrenalectomy in these cases have been superior to minimally invasive laparoscopy [26].

The disadvantages in these cases include the need for large muscle cutting incisions, significantly increased postoperative pain and longer recovery.

Adrenal metastases

The adrenal is a common site of metastatic disease in patients with cancers of other organs. The most common primary sites of origin are the lung, breast, kidney, gastrointestinal tract, and melanoma. About half of patients with an adrenal mass in the setting of known malignancy were found to have a metastasis to the adrenal gland [27]. With this in mind, careful evaluation for other adrenal primary tumours is still warranted to exclude functioning tumours. Most patients with metastases to the adrenal gland will also be found to have multiple sites of metastatic disease, but occasionally the adrenal will be the site of a solitary metastasis. Most patients are asymptomatic with the adrenal mass noted incidentally on imaging, but occasionally patients will experience back or flank pain from a large adrenal lesion (Fig. 4).

Imaging of suspected adrenal metastases is similar to other adrenal masses, although comparison with previous imaging is particularly important to confirm recent occurrence as well as growth of the lesion. Needle biopsy of suspected metastatic lesions of the adrenal confirms the diagnosis if a positive biopsy is obtained,

Figure 4 Solitary adrenal metastasis in a patient with previous history of treated ovarian carcinoma. Patient was symptomatic with flank pain necessitating an open adrenalectomy.

but a negative biopsy is less helpful. The overall risk/value of the biopsy has to be considered within the clinical context for each particular patient.

The decision to undergo adrenalectomy for metastasis should be undertaken carefully, taking into account several factors including the availability of non-surgical and systemic options. The best overall results are obtained with solitary metastasis, longer disease-free interval from initial cancer diagnosis, and complete resection of the lesion [28]. Patients with favourable features had a reported 5-year survival of ~30%, whilst patients with metastasis from a kidney primary seemed to have better overall survival, which may be reflective of the unpredictable biological behaviour of renal cancer [29]. Minimally invasive adrenalectomy is an attractive approach for patients with metastatic disease, offering equivalent oncological outcomes with minimal patient morbidity [30].

Partial adrenalectomy

Complete removal of the adrenal gland is commonly performed for surgical adrenal disease. This approach subjects patients without any remaining functional adrenal tissue to a complicated lifelong regimen of hormone replacement with both mineralocorticoid and adrenocorticoid. Adrenal-sparing surgery (partial adrenalectomy) has been introduced as an alternative approach to prevent surgically induced adrenal insufficiency. This approach is indicated in patients with bilateral adrenal masses, mass in a solitary adrenal gland, or patients with hereditary syndromes that predispose them to future development of adrenal masses (e.g. multiple endocrine neoplasia type 2 – MEN2). Partial adrenalectomy is also a reasonable approach in an elective setting for patients with a unilateral small adrenal tumour that is not suspicious for malignancy, like small aldosterone or cortisol secreting adenomas.

Similar to the general trend in surgical adrenalectomy, partial adrenalectomy is performed using minimally invasive techniques in the overwhelming majority of cases, as the technique was described [31]. Using standard laparoscopy or robotic assistance has become the most common technique for partial adrenalectomy, and LESS surgery has been used successfully as well. All minimally invasive techniques have reported technically successful surgery with adequate excision of tumour and preservation of adrenal function in most cases. A large retrospective series comparing (retroperitoneal) laparoscopic partial (100 cases) versus total adrenalectomy (220 cases) confirmed the utility of the procedure with adequate adrenal function in 14 of 15 patients with bilateral disease [32].

The technique of partial adrenalectomy involves visualisation of the adrenal gland and identification of the mass within the adrenal gland. Intraoperative ultrasonography can be used to identify smaller subtle lesions. The tumour is usually resected without vascular control taking care to avoid entering the tumour capsule. Haemostasis of the remnant adrenal is obtained by clips, electrocoagulation, or a variety of energy coagulation devices.

Conclusion

Adrenal masses are frequently encountered in urological practice and may present a diagnostic and management dilemma. Adequate clinical and radiological assessment frequently results in identifying masses that require surgical treatment for hyperfunction or suspected malignancy. Urologists should be adept at managing adrenal masses using laparoscopic or open surgical techniques. Adequate pre- and postoperative management of patients with adrenal masses is essential to minimising the patient's perioperative morbidity.

Conflict of interest

None.

References

[1] Angeli A, Osella G, Alì A, Terzolo M. Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group. *Horm Res* 1997;**47**:279–83.

[2] Bovio S, Cataldi A, Reimondo G, Sperone P, Novello S, Berruti A, et al. Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. *J Endocrinol Invest* 2006;**29**: 298–302.

[3] Hamrahian AH, Ioachimescu AG, Remer EM, Motta-Ramirez H, Bogabathina H, Levin HS, et al. Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. *J Clin Endocrinol Metab* 2005;**90**: 871–7.

[4] Caoili EM, Korobkin M, Francis IR, Cohan RH, Platt JF, Dunnick NR, et al. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. *Radiology* 2002;**222**:629–33.

[5] Haider MA, Ghai S, Jhaveri K, Lockwood G. Chemical shift MR imaging of hyperattenuating (>10 HU) adrenal masses: does it still have a role? *Radiology* 2004;**231**:711–6.

[6] Young Jr WF. Clinical practice. The incidentally discovered adrenal mass. *N Engl J Med* 2007;**356**:601–10.

[7] Sturgeon C, Shen WT, Clark OH, Duh QY, Kebebew E. Risk assessment in 457 adrenal cortical carcinomas: how much does tumor size predict the likelihood of malignancy? *J Am Coll Surg* 2006;**202**:423–30.

[8] Maurea S, Mainenti PP, Romeo V, Mollica C, Salvatore M. Nuclear imaging to characterize adrenal tumors: comparison with MRI. *World J Radiol* 2014;**6**:493–501.

[9] Charbonnel B, Chatal JF, Ozanne P. Does the corticoadrenal adenoma with "pre-Cushing's syndrome" exist? *J Nucl Med* 1981;**22**:1059–61.

[10] Young Jr WF. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. *Endocrinol Metab Clin North Am* 2000;**29**:159–85.

[11] Barzon L, Fallo F, Sonino N, Boscaro M. Development of overt Cushing's syndrome in patients with adrenal incidentaloma. *Eur J Endocrinol* 2002;**146**(–6):61.1–6.1.

[12] Fassnacht M, Johanssen S, Quinkler M, Bucsky P, Willenberg F, Beuschlein F, et al. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. *Cancer* 2009;**115**:243–50.

[13] Bellantone R, Ferrante A, Boscherini M, Lombardi CP, Crucitti F, Crucitti F, et al. Role of reoperation in recurrence of adrenal cortical carcinoma: results from 188 cases collected in the Italian National Registry for Adrenal Cortical Carcinoma. *Surgery* 1997;**122**:1212–8.

[14] Porpiglia F, Fiori C, Daffara FC, Zaggia B, Ardito A, Scarpa RM, et al. Does nephrectomy during radical adrenalectomy for stage II adrenocortical cancer affect patient outcome? *J Endocrinol Invest* 2016;**39**:465–71.

[15] Reibetanz J, Jurowich C, Erdogan I, Nies C, Rayes N, Dralle H, et al. Impact of lymphadenectomy on the oncologic outcome of patients with adrenocortical carcinoma. *Ann Surg* 2012;**255**:363–9.

[16] Autorino R, Bove P, De Sio M, Miano R, Micali S, Cindolo L, et al. Open versus laparoscopic adrenalectomy for adrenocortical carcinoma: a meta-analysis of surgical and oncological outcomes. *Ann Surg Oncol* 2016;**23**:1195–202.

[17] Terzolo M, Angeli A, Fassnacht M, Daffara F, Tauchmanova L, Conton PA, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007;**356**:2372–80.

[18] Berruti A, Fassnacht M, Baudin E, Hammer G, Haak H, Leboulleux S, et al. Adjuvant therapy in patients with adrenocortical carcinoma: a position of an international panel. *J Clin Oncol* 2010;**28**:e401–2, author reply e403.

[19] Gagner M, Lacroix A, Bolté E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *N Engl J Med* 1992;**327**:1033.

[20] Kebebew E, Siperstein AE, Duh QY. Laparoscopic adrenalectomy: the optimal surgical approach. *J Laparoendosc Adv Surg Tech A* 2001;**11**:409–13.

[21] Miccoli P, Raffaelli M, Berti P, Materazzi G, Massi M, Bernini G. Adrenal surgery before and after the introduction of laparoscopic adrenalectomy. *Br J Surg* 2002;**89**:779–82.

[22] Taskin HE, Siperstein A, Mercan S, Berber E. Laparoscopic posterior retroperitoneal adrenalectomy. *J Surg Oncol* 2012;**106**:619–21.

[23] Winter JM, Talamini MA, Stanfield CL, Chang DC, Hundt JD, Dackiw AP, et al. Thirty robotic adrenalectomies: a single institution's experience. *Surg Endosc* 2006;**20**:119–24.

[24] Hirasawa Y, Miyajima A, Hattori S, Miyashita K, Kurihara I, Shibata H, et al. Laparoendoscopic single-site adrenalectomy versus conventional laparoscopic adrenalectomy: a comparison of surgical outcomes and an analysis of a single surgeon's learning curve. *Surg Endosc* 2014;**28**:2911–9.

[25] Leboulleux S, Deandreis D, Al Ghuzlan A, Aupérin A, Goéré D, Dromain C, et al. Adrenocortical carcinoma: is the surgical approach a risk factor of peritoneal carcinomatosis? *Eur J Endocrinol* 2010;**162**:1147–53.

[26] Mir MC, Klink JC, Guillotreau J, Long JA, Miocinovic R, Kaouk JH, et al. Comparative outcomes of laparoscopic and open adrenalectomy for adrenocortical carcinoma: single, high-volume center experience. *Ann Surg Oncol* 2013;**20**:1456–61.

[27] Lenert JT, Barnett Jr CC, Kudelka AP, Sellin RV, Gagel RF, Prieto VG, et al. Evaluation and surgical resection of adrenal masses in patients with a history of extra-adrenal malignancy. *Surgery* 2001;**130**:1060–7.

[28] Gittens Jr PR, Solish AF, Trabulsi EJ. Surgical management of metastatic disease to the adrenal gland. *Semin Oncol* 2008;**35**:172–6.

[29] Lau WK, Zincke H, Lohse CM, Cheville JC, Weaver AL, Blute ML. Contralateral adrenal metastasis of renal cell carcinoma: treatment, outcome and a review. *BJU Int* 2003;**91**:775–9.

[30] Strong VE, D'Angelica M, Tang L, Prete F, Gönen M, Coit D, et al. Laparoscopic adrenalectomy for isolated adrenal metastasis. *Ann Surg Oncol* 2007;**14**:3392–400.

[31] Janetschek G, Lhotta K, Gasser R, Finkenstedt G, Jaschke W, Bartsch G. Adrenal-sparing laparoscopic surgery for aldosterone-producing adenoma. *J Endourol* 1997;**11**:145–8.

[32] Walz MK, Peitgen K, Diesing D, Petersenn S, Janssen OE, Philipp T, et al. Partial versus total adrenalectomy by the posterior retroperitoneoscopic approach: early and long-term results of 325 consecutive procedures in primary adrenal neoplasias. *World J Surg* 2004;**28**:1323–9.