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Review

"State of the Art" Management of Adrenal Masses – "How to Do It?"

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Abstract
By the frequent use of computed tomography or ultrasound the detection of incidentally found adrenal tumours has become a common problem. This is also reflected in the worldwide proliferation of literature over the past decades. Most incidentally-found adrenal tumours are benign non-functioning cortical adenomas. But benign functioning tumours producing aldosterone, cortisol or catecholamines, adrenocortical carcinoma or adrenal gland metastasis can also be found. Surgical therapy is always indicated in case of hormonal overproduction or in case of suspected adrenocortical carcinoma; in all other cases the correct and adequate therapeutic approach is still under debate and a controversial topic of discussion. This review deals with the different forms of adrenal tumours regarding the optimal diagnostic and therapeutic approach to give physicians an easy-to-follow guideline.

Key words: adrenal mass, incidentaloma, treatment, endoscopic adrenalectomy

Abbreviations: ACC: adrenal cortical carcinoma; ARR: aldosterone – renin – ratio; CS: Cushing's syndrome; CT: computed tomography; MRI: magnetic resonance imaging; NIH: National Institutes of Health; PA: primary aldosteronsim; PAC: plasma aldosterone concentration; PCC: pheochromocytoma; PRA: plasma renin activity

Adrenal incidentalomas are defined as "clinically silent masses discovered incidentally during imaging procedures, performed for unrelated nonadrenal problems". With the increasingly widespread use of highly sensitive imagery with improved image resolution, the accidental detection of an incidentaloma has become a frequent clinical problem (Brunt and Moley 2001). Based on autopsy studies adrenal nodules have been recognised for decades, with an overall frequency of approximately 6% (Thompson and Young 2003). Today adrenal lesions can be found in up to 3% of all computed tomography scans of the thorax or abdomen (Brunt and Moley 2001). The clinical problems of the correct treatment of adrenal tumours are reflected in the worldwide proliferation of literature over the past decades. The incidence of incidentaloma correlates with the age of the patients and mostly occurs in people older than 50 years (Brunt and Moley 2001). This may be due to the increasing frequency in the use of imaging methods on older patients and the slow development of incidentalomas. A different explanation is a compensatory growth of adrenal nodules due to ischemic disease caused by hypertension or diabetes mellitus frequently found in older people (Mantero et al. 2000). This theory correlates with the higher number of patients with hypertension, obesity and diabetes mellitus amongst those with an incidentaloma than in the overall population, but it cannot be excluded that patients with cardiovascular risk factors are more often exposed to imaging methods. The spectrum of incidentalomas ranges from a benign nonfunctioning cortical adenoma that necessitates no further therapy to an adrenocortical carcinoma that has a worse prognosis despite aggressive surgical therapy. Imaging procedures are carried out either during staging or follow-up of a malignant disease or for the purpose of further diagnostics for a nonmalignant disease. The underlying pathology is strongly correlated with the indication for the imaging work-up.

In patients without known extra-adrenal malignancy, the overwhelming majority of incidentalomas (up to 80%), are nonfunctional adrenal adenomas, but nearly 40 different diagnoses have been associated with adrenal incidentalomas (Thompson and Young 2003). The next step in the correct diagnostic approach is to discriminate between adrenal adenomas and carcinomas and depends on the imaging method that was initially used and detected the adrenal incidentaloma. Adrenal cortical carcinoma is a rare and highly malignant tumour with a worldwide annual incidence of approximately 0.5 – 2 cases per million. This low incidence contrasts strongly with the high incidence of benign adrenal lesions and incidentalomas (Schulick and Brennan 1999, Dackiw et al. 2001). Due to nonspecific signs and the inaccessibility for a clinical examination of the adrenal glands, up to 70% of the patients are diagnosed at an advanced clinical stage of III or IV (Ng and Libertino 2003) and in 40% of patients metastases had developed with the lung and liver being the most frequent sites (Schulick and Brennan 1999, Ng and Libertino 2003). The challenge one is faced with is to avoid overlooking a small nonfunctioning adrenal cortical carcinoma, without perform-

ing too many adrenalectomies for benign inactive adrenal tumours, because only a surgical approach, which is obviously connected with morbidity and mortality, can confirm the correct diagnosis of a benign adrenal lesion. In ACC the occurrence of clinical symptoms strongly depends on the ability to secrete hormones that can be seen in approximately 40% to 70% of the patients and on the size of the tumour (Dackiw et al. 2001). Symptoms in endocrine active tumours include virilization in women, classical stigmata of Cushing's syndrome in both sexes or a mixture of both, whereas pure hyperaldosteronism is rarely found in functioning tumours (Schulick and Brennan 1999). Nonspecific abdominal discomfort or pain as a result of rapid growth, significant tumour size or local invasion is the major symptom in patients with nonfunctioning tumours (Schulick and Brennan 1999). The clinical picture of functioning tumours can vary due to the changing quality or quantity of hormone production (Wajchenberg et al. 2000). A different clinical sign in patients with ACC is the rapid onset of symptoms with a mean duration of less than one year, regardless of functional status (Dackiw et al. 2001).

The expressiveness of abdominal ultrasound strongly depends on the skills of the examiner, since primary tumours of the retroperitoneum, stomach and tail of the pancreas can sometimes be mistaken for adrenal tumours. An abdominal CT is the imaging method of choice to evaluate the origin of the lesion and to determine the risk of malignancy with reasonable and high certainty by defining the maximum size and certain imaging features. In contrast to adrenal adenoma, adrenocortical carcinoma usually presents with irregular borders, focal areas of haemorrhage and necrosis, invasion of adjacent structures and lymphadenopathy. Another feature of the CT for the evaluation of the significance are the Hounsfield units and the washout performance. Benign adrenal adenomas almost exhibit CT attenuation values of less than 10 Hounsfield units, but tumours with attenuation values of greater than 10 Hounsfield units are not automatically malignant (Nwariaku et al. 2001). Kebapci et al. could show that the absolute or relative percentage washout of contrast material on delayed contrast-enhanced CT is a highly specific test for the differentiation of lipid-poor and lipid-rich adrenal adenomas from adrenal non-adenomas (Kebapci et al. 2003). Therefore, if the lesion located in the adrenal gland is first detected by ultrasound, an abdominal computed tomography should be carried out, too. For lesions such as cysts or myelolipoma that can clearly be identified with the imaging methods no further diagnostic imaging modality is necessary (Shen et al. 2005). For differentiation of the significance additional information can be obtained by using magnetic resonance imaging that offers the advantage of viewing the tumour relationship to the adjacent organs in multiplanar planes and on the basis of signal intensity of the lesion on T1- and T2-weighted images. With the use of MRI an infiltration or a tumour thrombus in the renal vein or the inferior vena cava can be revealed or excluded because ACC resembles renal cell adenocarcinoma in its ability to develop vena cava tumour thrombus extensions either by direct invasion or more commonly by intraluminal extension via the adrenal or renal vein (Ng and Libertino 2003, Meyer et al. 2004). In addition to the conventional spin-echo MRI, gadolinium-enhanced MRI and chemical shift imaging MRI can be used for further differentiation of the adrenal lesion.

In patients suffering from a known extra-adrenal malignant disease the incidence of adrenal gland metastasis is as high as 27% and depends on the degree of probability that this malignancy will metastasize to the adrenal glands (Mansmann et al. 2004). Mainly lung cancer, but also breast cancer, colon cancer, renal cell cancer and melanoma metastasize to the adrenal gland. In most of the patients the adrenal enlargement is diagnosed synchronously with the diagnosis of a primary tumour and other metastases, but metachronous development is also encountered. An adrenal gland metastasis should be expected in every patient with known extra-adrenal malignancy presenting with an adrenal lesion, especially if the adrenal tumour is larger than 2 cm or if bilateral adrenal tumours are found. If the adrenal gland tumour cannot be confirmed with high reliability by the imaging features in patients with known extra-adrenal malignancy, and if it has any impact on further therapy, an image-guided fine-needle biopsy, an invasive method, can be used to differentiate between adrenal gland tissue and metastatic tissue. However, this procedure is not an adequate diagnostic method for the differentiation between an adrenal adenoma and an adrenal carcinoma, because it is not possible to evaluate certain histological criteria of malignancy from a sole cytological specimen (Brunt and Moley 2001).

Next to these imaging features, the maximum size of the adrenal lesion is regarded as one of the major risk factors for malignancy because the majority of ACCs presumably have a size of over 6 cm due to fast growth, and the risk of malignancy increases with the size of the tumour ranging from 2% for lesions < 4 cm to more than 25% for lesions exceeding 6 cm in size (Shen et al. 2005). The NIH state-of-the-science statement suggests that patients with tumours greater than 6 cm usually are treated surgically, while those with tumours smaller than 4 cm are generally monitored. In patients with tumours between 4 and 6 cm, criteria in addition to size should be considered in making the decision to monitor or proceed to adrenalectomy. In patients with tumours that remain stable in two imaging studies carried out at least 6 months apart and do not exhibit hormonal hypersecretion over 4 years, further follow-up may not be warranted (NIH state-of-the-science statement of management of the clinically inapparent adrenal mass ("incidentaloma")). Regarding the available published literature, various recommendations for surgical treatment have been made with removal indicated in the case of a diameter of more than 3, 4, 5 and 6 cm. However, size of the incidentaloma determined by imaging should be assessed with care, because this was often underestimated (Lau et al. 2004). On the other hand, the determination of a clinically significant change in size and the validation of the reproducibility of the measurements have to be defined. In all adrenal lesions a tendency towards growth in intervals or a very slow growth

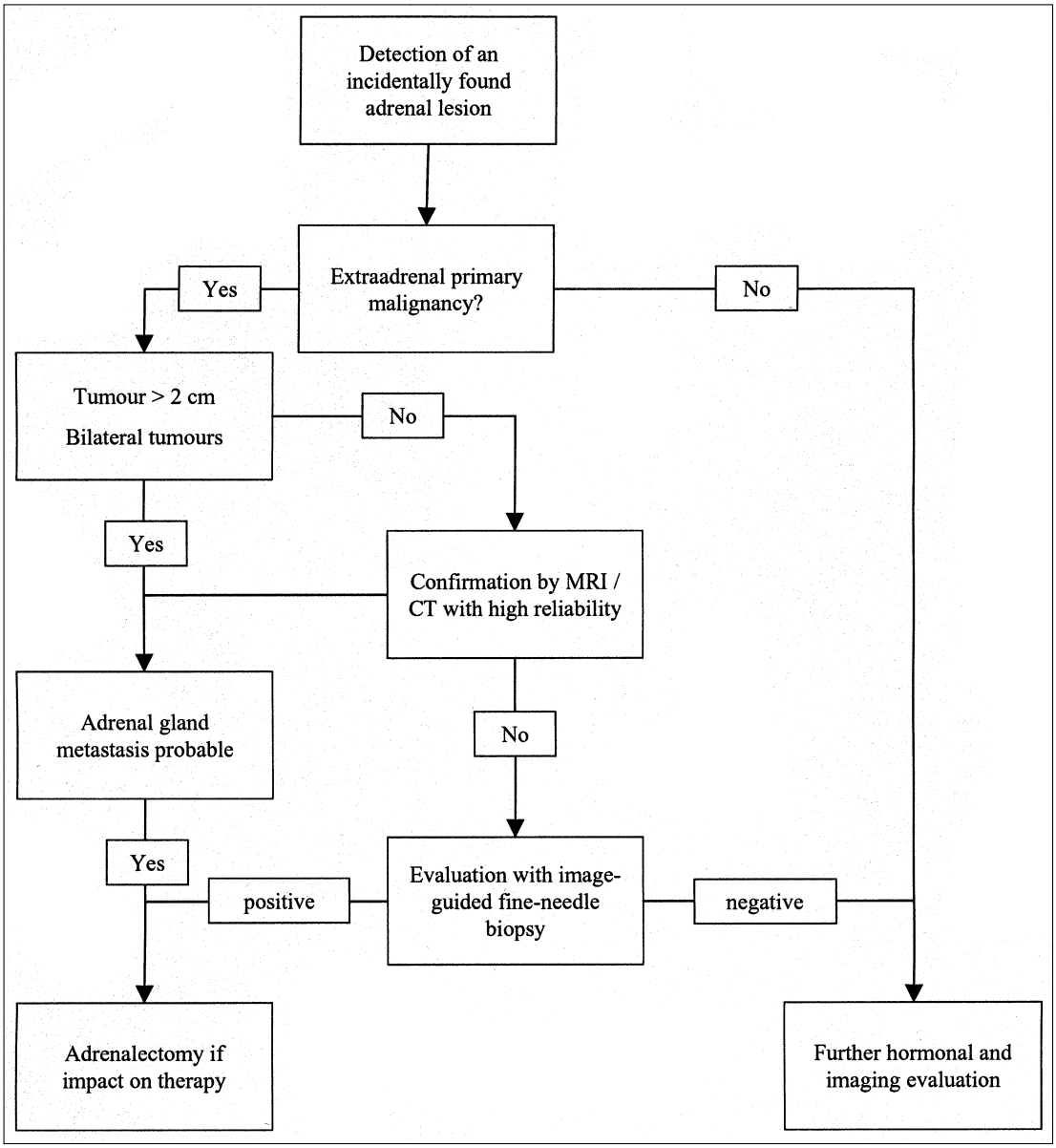

Fig. 1. Evaluation of an adrenal mass in patients without known extra-adrenal malignancy.

must be assumed, because they have grown more or less fast and will have at some time reached their present size. Since the reason for the development and the behaviour regarding the growth remains unclear, it can be postulated that every incidentaloma can grow until a diameter of 4 or 6 cm is exceeded if one waits long enough in young patients, and the indication for surgical removal of the incidentaloma in relation to the extent of growth is unclear. Therefore, criteria in addition to size and tumour features in the imaging methods that should be taken into consideration are the individual patient's general condition, the patient's fear of malignancy and especially the age of the patient. In patients with adrenal lesions larger than 4 cm without any sign of malignancy the therapy should be individualized. Especially in patients younger than 50 years of age with adrenal lesions exceeding 4 cm in size a surgical approach should be used because a repeated and life-long close follow-up in the case of an anxious patient who is informed of the diagnosis will sometimes exceed the cost of a single operation.

If an adrenocortical carcinoma can be ruled out by imaging features and a benign adrenal lesion is assumed, the next step in the diagnostic approach is to determine a possible endocrine activity of the lesion. Renin-independent overproduction of aldosterone leads to the clinical picture of primary aldosteronism that is characterised by drug resistant hypertension with a maximum systolic pressure of 180 - 200 mmHg and hypokalemia with a minimum mean level of 2.5 – 3 mmol/L. PA is caused by adrenal adenoma in 75% or by bilateral micro- or macronodular hyperplasia in 25% of the patients. Aldosterone-secreting adrenal adenomas typically measure 0.5-2 cm in size and present as well-circumscribed tumours, whereas hyperplasia presents with bilateral enlargement of the adrenal glands in computed tomography (Ganguly 1998). Adrenal vein sampling should no longer be used today

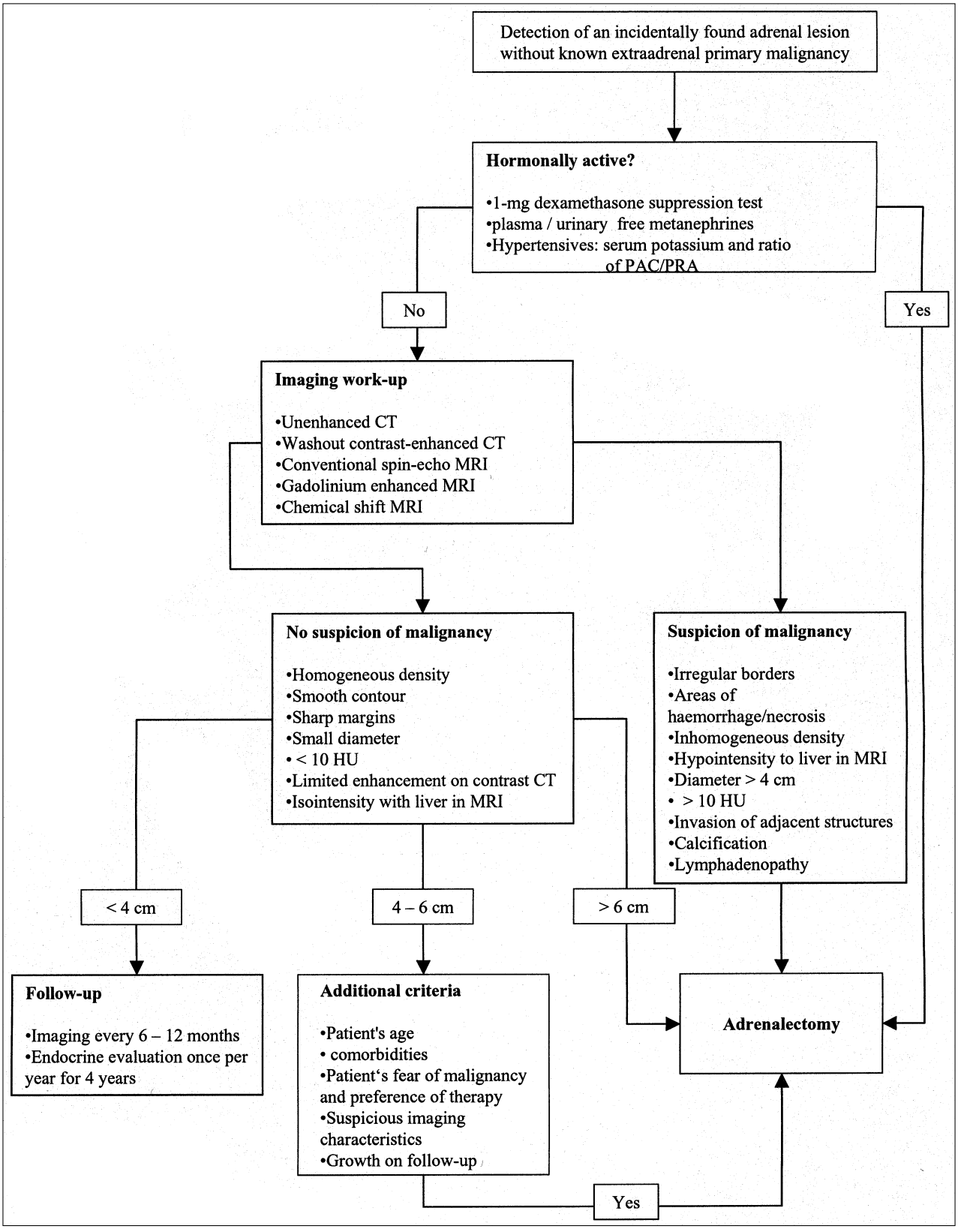

Fig. 2. Evaluation of an adrenal mass in patients with known extra-adrenal malignancy.

in routine testing for the differentiation of unilateral adenoma and bilateral hyperplasia because the results from this invasive method depend upon the skill and experience of the radiologist, and is connected to side effects, such as adrenal haemorrhage (Magill et al. 2001, Harris et al. 2003). Other tumour entities, such as adrenal aldosterone-producing carcinoma, unilateral hyperplasia or glucocorticoid-remediable aldostero-

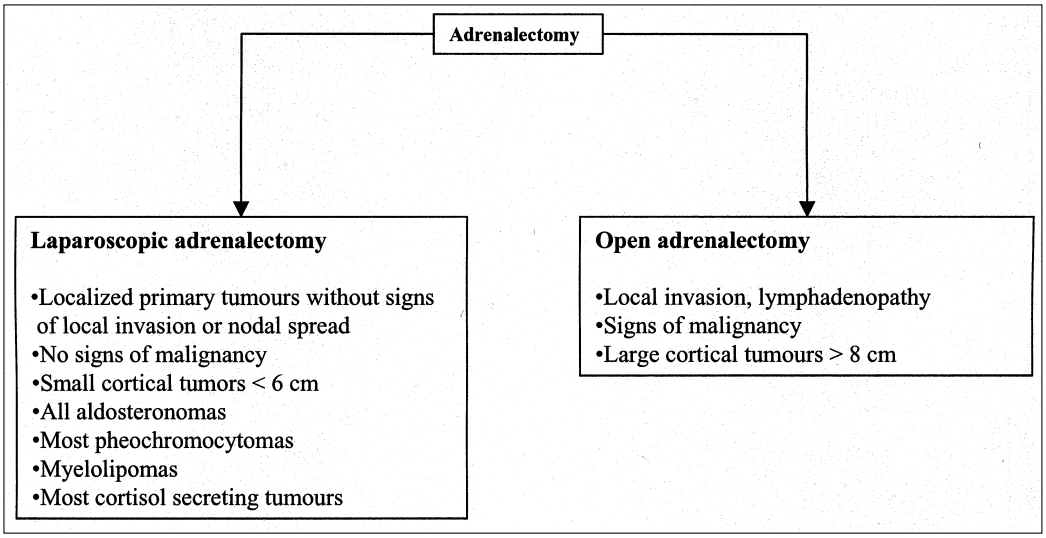

Fig. 3. Criteria for open vs. endoscopic approach for adrenalectomy.

nism are very rare, with a frequency of less than 1% (Wheeler and Harris 2003). First reported by Jerome W. Conn in 1955, PA is one of the potentially curable forms of hypertension with an estimated prevalence of around 0.5% – 2.5% in the hypertensive population (Ganguly 1998, Wheeler and Harris 2003). Additional symptoms include hypernatriemia, alkalosis and hypochloremia (Harris et al. 2003). Hypertension is the most important factor concerning morbidity and quality of life, including acute or chronic cardiovascular or cerebrovascular complications. Hypertension is the first and major symptom, hypokalemia occurs later in the course of the disease caused by increased autonomous hormone production. Many years can pass from the onset of hypertension to the establishment of the correct diagnosis at the simultaneous occurrence of hypertension and hypokalemia and subsequent surgery, with the patients being insufficiently treated with various antihypertensive agents such as essential hypertensives during this time (Meyer et al. 2005). Today's screening test of choice is measurement of serum potassium level, plasma aldosterone concentration and plasma renin activity by calculating the Aldosterone–Renin–Ratio first introduced by Hiramatsu (Hiramatsu et al. 1981). If the ARR is above 300 pg/mL per ng/mL/h, the correct diagnosis of PA is possible at an early stage of the disease with only small autonomous hormone secretion and plasma aldosterone concentration, plasma renin activity and the serum potassium level still within the normal limits. The calculation of the ARR should always be combined with an absolute cut-off level of 150 pg/mL for PAC because the ARR may also be increased in patients with low-renin essential hypertension (Ganguly 1998). The diagnosis of PA should be suspected in young hypertensive patients refractory to two or more standard antihypertensive agents. If these criteria are fulfilled, a salt loading test should be carried out for confirmation of the diagnosis that will show no suppression of PAC after several hours of saline infusion in patients with PA (Wheeler and Harris 2003). Using the ratio makes PA one of the most common surgically treatable and potentially curable forms of hypertension. After making the correct diagnosis of PA, the next step is the identification of the surgically correctable form by means of the orthostasis test. If an adrenal adenoma can be clearly diagnosed, resection should be carried out using an endoscopic approach; if bilateral enlargement can be seen, medical treatment with spironolactone should be applied.

Patients suffering from autonomous secretion of glucocorticoids show a varied constellation of clinical abnormalities depending upon the amount and duration of the cortisol excess, such as moon facies, weight gain with central obesity, plethora, purple striae, fragile skin, hypertension, glucose intolerance, and buffalo hump (Boscaro et al. 2001). The clinical picture known as Cushing's syndrome was first described by Boston neurosurgeon Harvey Cushing in 1932. This endocrine disorder has an annual incidence of approximately 10 patients per 1 million people and can be further classified in ACTH-dependent form that occurs with a frequency of 70% - 80%, and ACTH-independent form with a frequency of 20% – 30% (Orth 1995, Boscaro et al. 2001). In both forms women are more often affected at a ratio of around 6:1 (van Heerden et al. 1995). The ACTH-dependent form can be caused by pituitary adenoma (also known as Morbus Cushing) or an ectopic ACTH-secreting tumour. Resection of the ACTH-secreting source is the treatment of choice. The ACTH-independent form can be caused by adrenal adenoma, adrenal carcinoma and primary macro- or micronodular hyperplasia (van Heerden et al. 1995). High-dose exogenous steroid medication can also cause CS. The mortality of patients with untreated hypercortisolism is high with a rate of up to 50% within a period of 5 years due to infections, hypertensive crisis with cardiac infarction and thrombembolism (Imai et al. 1996). Additionally, patients with CS are in a poor preoperative condition due to the high amount of fat, poor wound healing and the risk of thrombembolism, with a morbidity of 2%– 20% and a mortality of 0%– 10% (van Heerden et al. 1995, Meyer and Behrend 2004). Therefore, an early diagnosis is essential to reduce intra- and postoperative complications and the morbidity and mortality (Meyer and Behrend 2004). To rule out overproduction of cortisol, the 24-hour urinary cortisol concentration and the daily plas-

ma cortisol rhythm should be measured. The low-dose (1 mg) dexamethasone suppression test that shows a non-suppressible plasma cortisol concentration in patients with autonomous glucocorticoid secretion can also be used as a screening test. After establishing the diagnosis with the use of these measurements, the concentration of ACTH should be measured to distinguish between the ACTH-dependent and ACTH-independent form. In up to 10% of patients with incidentalomas, an increased cortisol concentration and a pathologic low-dose dexamethasone suppression can be detected without any clinical signs of hormonal overproduction. In these patients with so-called subclinical hypercortisolism, a surgical approach is also justified because these patients are at risk of developing overt CS (Ross 1994, Shen et al. 2005).

Pheochromocytomas are rare catecholamine-secreting tumours with their origin in chromaffin cells of the sympathetic nervous system and mostly arise from the adrenal medulla (Bouloux and Fakeeh 1995). Due to their inadequate and unpredictable excessive secretion of catecholamines, PCCs endanger the patients with clinical symptoms such as hypertensive crisis, headache, palpitations and anxiety due to the consequences of a catecholamine excess. Because of the nonspecific symptoms the correct diagnosis is often delayed (Mannelli et al. 1999). Long-term symptoms of the unrecognised disease are cardiac insufficiency, atherosclerosis, cerebral apoplexy and cardiomyopathy. Most of the PCCs are benign tumours, with approximately 10% of all PCCs malignant (Proye et al. 1994). Measurement of urinary free metanephrines remains the standard laboratory procedure for the biochemical diagnosis of pheochromocytoma. The determination of plasma catecholamines for reliable pheochromocytoma detection has been discarded due to its limited sensitivity and specificity (Lenders et al. 2002). As an additional examination, Chromogranin A and B can be used (Boomsma et al. 1995). In addition to the imaging modalities mentioned above, 131I-MIBG scintigraphy can be used. 131I-MIBG scanning has a high diagnostic accuracy in pheochromocytoma detection with a high sensitivity and has a superior diagnostic value for extra-adrenal paragangliomas. Because the patients are endangered by sudden catecholamine excess which could be triggered by tumour manipulation during surgery, an efficient pharmacological premedication with phenoxybenzamine and intraoperative blood pressure management should be applied (Sand et al. 1997).

A surgical therapy is always indicated in case of hormonal overproduction or in case of suspected malignancy. The surgical therapy of choice for incidentalomas and for benign endocrine active adrenal tumours is the endoscopic adrenalectomy. In 1992 Gagner performed the first endoscopic adrenalectomy and demonstrated the superiority of this approach over open surgery (Gagner et al. 1992). The technical advances and surgical experiences in minimally invasive techniques today are the gold standard for benign lesions as a gentle surgical technique in terms of postoperative recovery, pain, anxiety, length of hospital stay, morbidity, mortality and the overall costs and has replaced the conventional dorsal approach (Mannsmann et al. 2004). The conventional dorsal approach - the gold standard for the excision of small benign adrenal lesions prior to the introduction of the endoscopic approach - should no longer be taken. By using the retroperitoneoscopic approach, a partial adrenalectomy can also safely be carried out without diminishing the results in the long-term follow-up (Walz et al. 2004). A relative contraindication for endoscopic adrenalectomy is a benign tumour with a maximum size exceeding 10-12 cm. However, the endoscopic removal of larger tumours is possible of course, and the effectiveness and safety have been demonstrated by some authors (Porpiglia et al. 2002, Walz et al. 2005). The indications for endoscopic adrenalectomy though should not be changed because of the availability of a gentle surgical approach, but the selection criteria formerly used can be adopted today for the endoscopic approach (Brunt and Moley 2001). In patients with hormonally active benign adrenal tumours, a life-long regular control of the blood pressure and the antihypertensive medication is necessary. The preoperative duration and seriousness of the elevated blood pressure may be connected to significant and irreversible end-organ damage and vascular changes leading to persistent postoperative hypertension (Simon et al. 1993, Sapienza and Cavallaro 1999, Sywak and Pasieka 2002, Sawka et al. 2001, Meria et al. 2003, Harris et al. 2003, Meyer et al. 2005).

If an adrenocortical carcinoma is expected, an endoscopic approach is contraindicated and the transperitoneal transabdominal approach should be taken, because it facilitates the maximum exposure necessary for complete resection. If the malignancy is confined to the adrenal gland, endoscopic resection may be feasible if the principles of oncological surgery are respected, but long-term follow-up is needed to validate this approach (Porpiglia et al. 2004, Cobb et al. 2005). However, most adrenal cortical carcinomas infiltrate surrounding tissues, and resection of flanking tissues and organs is necessary that is most suitable done by an open transabdominal approach (Shen et al. 2004, Meyer et al. 2005, Roman 2006). The prognosis for untreated patients is very poor with a mean survival of only 3–6 months. An incomplete resection and the presence of metastases are the most unfavourable prognostic factors (Icard et al. 2001). Patients with an incomplete resection have a mean survival rate of about one year, with a 5-year survival rate of 0% – 9%. Therefore, because of the limited survival rate in patients with incomplete resections, and also in patients with an advanced stage of disease, the mainstay of therapy and only potentially curative treatment is the radical surgical resection of the tumour, the lymph nodes, any adjacent organ involved, the tumour thrombus in the inferior caval vein and even solitary metastases wherever possible (Dackiw et al. 2001, Ng and Libertino 2003). Metastases can be resected during the same operation by means of hemihepatectomy or lobectomy whereas a routine resection of the kidney produced no improved survival prospects (Schulick and Brennan 1999). This improves the prognosis and results in a 5-year survival period of 20% – 60% depending on the distribution of the stages in the surgical series and relief from the symptoms, particu-

larly in patients with functioning tumours (Schulick and Brennan 1999, Meyer et al. 2004). However, the mean disease-free interval, even after curative operation, is only approximately 12 - 22 months (Icard et al. 2001, Bellantone et al. 1997). Even after complete surgical excision, 23% to 80% of patients develop locoregional relapse or distant metastases with the patients dying within one year after the first sign of recurrence or metastases without further treatment (Bellantone et al. 1997). In the case of locoregional recurrence, only re-operation with complete resection prolongs disease-free survival with a 5-year survival rate of 27% – 57 % compared to medical treatment with various chemotherapeutic agents with a 5-year survival rate of 0% – 8% (Icard et al. 2001, Bellantone et al. 1997, Meyer et al. 2004). The main agent in the cytotoxic treatment of ACC is mitotane (Luton et al. 1990). This drug is a derivate of the insecticide DDT, accumulates in the adrenal gland and causes direct necrosis of the adrenal gland. The long-term efficacy is low, only 20% - 30% of patients have a partial remission, but it has shown to be highly effective in functioning tumours by reducing hormonal oversecretion in 80% of patients. Main side effects are of the gastrointestinal and neurological type.

The indication for an adrenalectomy in case of adrenal gland metastasis strongly depends on the stage of the disease and can be justified if it has any impact on the further therapeutic approach. An adrenal metastasis that is confined to the adrenal gland with a size of less than 10 cm is amenable to endoscopic adrenalectomy. With the resection of solitary adrenal gland metastasis, a 5-year survival of 25% can be achieved. Prognostic factors are a disease-free interval of more than 6 months before occurrence of the metachronous isolated adrenal metastasis in patients with non-small cell lung cancer (Mercier et al. 2005)

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