

REVIEW

Bilateral Primary Adrenal Non-Hodgkin's Lymphoma and Primary Adrenocortical Carcinoma – Review of the Literature

Preoperative Differentiation of Adrenal Tumors

ALEXANDRA OZIMEK, JOACHIM DIEBOLD*, RAINER LINKE**, JENS HEYN***, KLAUS HALLFELDT AND THOMAS MUSSACK

Department of Surgery Innenstadt, University Hospital Munich–Campus Innenstadt Nussbaumstrasse 20, 80336 München, Germany

**Department of Pathology, University Hospital Munich–Campus Innenstadt Thalkirchner Str. 36, 80336 München, Germany*

***Department of Nuclear Medicine, University Hospital Munich–Campus Innenstadt Ziemssenstrasse 1, 80336 München, Germany*

****Department of Anaesthesiology, University Hospital Munich–Campus Großhadern Marchioninistr. 15, 81377 München, Germany*

Abstract. Most of the adrenal tumors that are incidentally detected are benign adenomas. The incidence of malignant adrenal tumors including adrenocortical carcinoma (ACC) and primary adrenal lymphoma (PAL) is rather low. As many patients with ACC and PAL are diagnosed at an advanced stage of disease, the overall survival time of both entities remains poor. The therapeutic strategies for both entities differ. Thus an early differentiation between ACC and PAL is necessary. Unfortunately hitherto preoperative diagnosis of potentially malignant adrenal masses is still a main problem in the treatment of adrenal tumors. We present the case of a 57-year-old male patient with ACC and the case of an 87-year-old male patient with PAL and provide a systematic comparison of the clinical and pathological features of both entities. In both cases clinical and radiological features resulted in an initially false diagnosis. Primary surgical therapy was performed in both patients. The patient with PAL died five months after initial surgery. The patient with ACC showed tumor progression with local and systemic recurrence despite adjuvant therapy with mitotane and additional surgical therapy. Prognosis of patients with ACC and PAL seems to be dependant on the ability to start accurate treatment without any time delay. We propose some guidelines for diagnosis and surgical management of adrenal tumors.

Key words: Adrenal tumor, Adrenocortical carcinoma, Primary adrenal lymphoma, Non-Hodgkin's lymphoma, Bilateral adrenal masses

(Endocrine Journal 55: 625–638, 2008)

THE adrenal gland is a frequent site of neoplastic disease. It is estimated that adrenal masses occur in about 9% of the entire population. Since the early 1980's the detection of adrenal lesions has increased with the expanding use of high-resolution imaging procedures [1, 2]. Once discovered, every adrenal tumor has to be defined to exclude hormonal dysfunction and malignancy. Neoplastic involvement of the adrenal gland may result from primary tumors originating from the

adrenal cortex or the adrenal medulla. Primary malignant tumors are adrenocortical carcinomas (ACC), primary adrenal lymphomas (PAL) and malignant pheochromocytomas. In addition, the adrenal glands are frequent sites for metastatic disease.

Adrenocortical carcinoma (ACC) is a rare endocrine neoplasm with a heterogeneous presentation. Diagnosis and accurate treatment can be greatly delayed due to the absence of specific clinical symptoms. Thus prognosis of ACC is generally poor [3, 4]. The rarity of the tumor has made it difficult to establish treatment guidelines. In stages I–III complete operative resection remains the only potentially curative treatment. However, local recurrence is frequent and particularly related to the violation of the tumor capsule. Adjuvant

Received: January 28, 2008

Accepted: February 2, 2008

Correspondence to: Alexandra OZIMEK, MD, Department of Surgery Innenstadt, Klinikum der Universität München, Nussbaumstrasse 20, 80336 München, Germany

treatment options have still not been convincingly established. Hitherto, the adrenolytic compound mitotane (alone or in combination with cytotoxic drugs or tumor bed radiation) remains the treatment of choice. Traditional cytotoxic chemotherapy alone has generally produced disappointing responses, implying the need for new therapies for this disease [3].

Primary adrenal non-Hodgkin's lymphoma (PAL) is a rare neoplastic disease with about 116 reports in the literature, so far. It should be considered in patients with bilateral enlargement of adrenal glands and rapidly progressive adrenal insufficiency [5–9]. Most of these tumors are highly aggressive and their treatment is still not satisfactory. Therapeutic modalities include multi-agent chemotherapy, surgery followed by chemotherapy and/or radiation therapy and central nervous system (CNS) prophylaxis [5, 7]. Usually, the prognosis of PAL patients is fatal with early death occurring during chemotherapy. However, complete and partial remissions with a longer mean duration of survival have been reported in some cases [5–7, 10].

Indeed the overall survival time in patients with these tumors seems to be dependant on the ability to establish diagnosis early in order to start accurate treatment without any time delay. Unfortunately hitherto preoperative differentiation between ACC and

PAL is still a main problem in the treatment of potentially malignant adrenal tumors.

Case Reports

Case 1

An 84-year-old male patient in good physical condition was admitted to our department for evaluation of a six-month history of significant weight loss and lumbar pain. There was no past history of carcinoma. Laboratory investigations showed normochromic, normocytic anaemia, increased CRP and increased lactate dehydrogenase serum levels (Table 1). Contrast-enhanced CT scan revealed splenomegaly and large bilateral adrenal masses without abdominal lymphadenopathy. Thoracic CT scan excluded any hilar or mediastinal lymphadenopathy. The additional 2-[(18)F] fluoro-2-deoxyglucose (FDG)-PET scan showed an intense FDG accumulation in both adrenal glands without abnormal FDG uptake in extraadrenal regions (Fig. 1). Considering a 10-year history of arterial hypertension, bilateral phaeochromocytomas were suggested, but endocrine evaluation revealed all serum hormones and fractionated urinary catecholamines

Table 1. Laboratory serum values in an male patient with bilateral primary adrenal non-Hodgkin's lymphoma (case 1) and a male patient (case 2) with adrenocortical carcinoma. (LDH = lactate dehydrogenase; LH = luteinizing hormone; FSH = follicle stimulating hormone; ACTH = adrenocorticotrophic hormone)

Parameter	Value case 1	Value case 2	Normal range
Hemoglobin (g/dl)	11.4	14	14–17
Hematocrit (%)	32	39.5	38–52
Leukocytes (N=)	5100	9000	4000–11000
Thrombocytes (N=)	296000	281000	150000–400000
CRP serum level (mg/dl)	2.54	4.83	<0.5
LDH (U/l)	445	1221	<250
Lactat (mmol/l)	0.9	1.1	0.5–2.2
Potassium (mmol/l)	3.9	3.6	3.5–5.0
Aldosterone (pg/ml)	<10	<10	10–160
Estradiol (pg/ml)	21.0	10	<45.0
Progesterone (ng/ml)	0.6	0.5	<0.5
Testosterone (ng/ml)	335	272	350–900
LH (U/l)	11.1	3.3	1–10
FSH (U/l)	8.9	7.9	1–10
Prolactine (μU/ml)	92.2	338	30–350
Cortisol (μg/dl)	12.7	6.4	4.0–19.0
Cortisol after ACTH (μg/dl)	14	20.1	23–58
Cortisol after DEXA (μg/dl)	0.9	0.3	<2

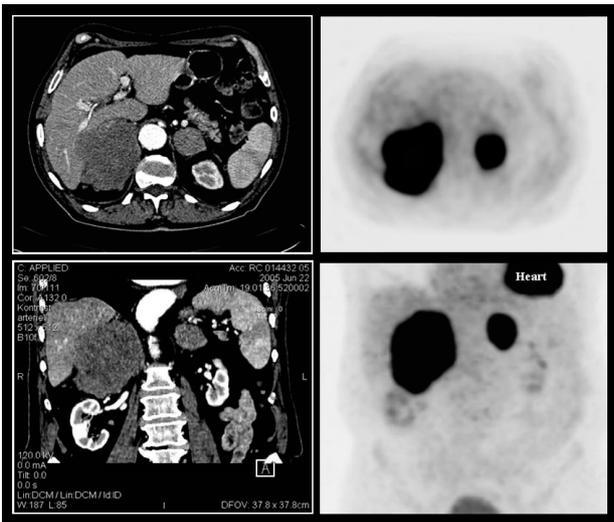


Fig. 1. Axial and sagittal PET CT scan of male patient with PAL. Intense FDG uptake in bilateral adrenal masses. The right adrenal mass is bigger than the left. There are no areas of abnormal FDG uptake.

within normal ranges. However, both non-hyperfunctioning adrenal masses were highly suggestive of malignancy because of the large diameter. Therefore fine needle aspiration (FNA) biopsy was avoided and open bilateral adrenalectomy with abdominal lymphadenectomy was performed. Histopathological examination revealed diffuse large cell non-Hodgkin's (NHL) lymphoma according to the World Health Organization Classification. The tumor cells were negative for Epstein-Barr virus (EBV) latent membrane protein-1 (LMP-1) and EB encoded RNA (EBER). After an uneventful postoperative period the patient was discharged at day 12 after surgery in good physical condition. Adjuvant chemotherapy therapy according to the CHOP-regime (cyclophosphamide, doxorubicin, vincristine, prednisone) was started. During the follow-up, the patient suddenly worsened four months postoperatively, and died another four weeks later because of disseminated progressive disease and cardiopulmonary failure.

Case 2

A 57-year-old male patient in good physical condition was referred to our clinic with complaints of left-sided abdominal and lumbar pain of two months duration.

Laboratory investigations showed highly increased

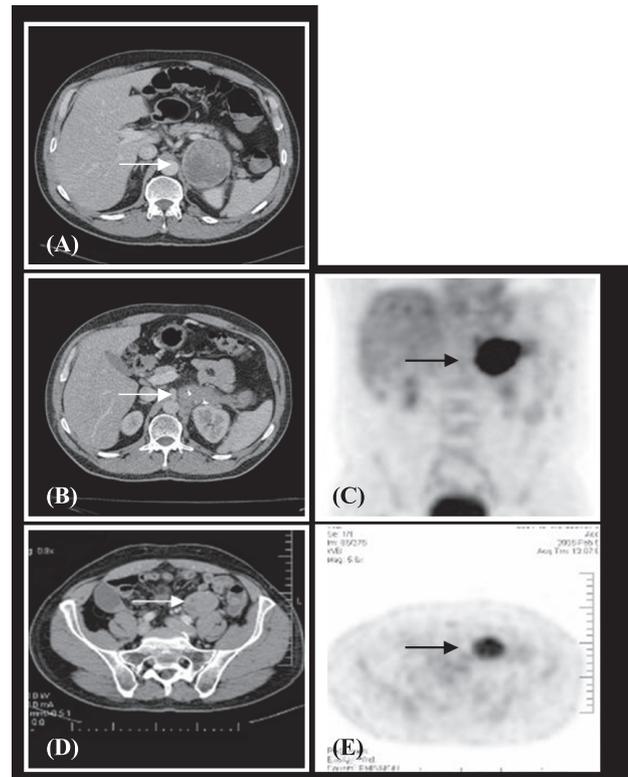


Fig. 2. Axial and sagittal PET CT scan of male patient with ACC showing primary tumor and progression of the disease. Fig. 3(A): Primary diagnosis of ACC in CT-abdomen scan. Fig. 3 (B–C): Axial and sagittal PET-CT scan of regional recurrence 11 months after laparoscopic adrenalectomy. Fig. 3 (D–E): Axial PET-CT scan of intraabdominal lymph node metastasis in the left spleno-renal region (D–E) 18 months after adrenalectomy.

CRP and lactate dehydrogenase serum levels as well as moderately increased liver enzymes (Table 1). Contrast-enhanced CT scan was performed and revealed a large adrenal tumor of the left adrenal gland with smooth margins but inhomogeneous enhancement after application of contrast medium. There was no evidence of abdominal lymphadenopathy (Fig. 2A). Thoracic CT scan did not show any hilar or mediastinal lymphadenopathy. A pheochromocytoma was excluded because the medical history was uneventful and all serum hormones as well as fractionated metanephrines and free catecholamines in a 24-hour urine specimen were within normal ranges. Due to the imaging studies showing localized disease without infiltrative growth or lymphadenopathy, a non-functioning incidentaloma was supposed and laparoscopic lateral adrenalectomy was performed. Intraoperatively, there

Table 2. Epidemiological, clinical and pathological features of PAL and ACC

Clinical features	PAL	ACC
Incidence	116 cases worldwide (1961–2006)	0.4/100 000
Mean Age [years]	68	10 & 50
Gender	w : m = 1 : 3	w : m = 1.5 : 1
Bilateral involvement [%]	70%	10%
Presenting symptoms	<ul style="list-style-type: none"> • symptoms of adrenal insufficiency • symptoms of lymphoma • symptoms of central nervous system involvement • unusual involvement of extranodal organs • rare symptoms (AIHA or thrombocytopenia, skin itching, hypercalcaemia) • B symptoms 	<ul style="list-style-type: none"> • symptoms of endocrine excess • symptoms of large tumor (abdominal discomfort, abdominal pain / lumbar pain) • B symptoms
CT-Results	<ul style="list-style-type: none"> • large mass • variable density 	<ul style="list-style-type: none"> • large mass • central necrosis or calcification • heterogeneous enhancement • infiltration of adjacent organs • lymph node or other metastases (lung and liver)
MRT-Results	<ul style="list-style-type: none"> • low signal intensity on T1 -weighted images • high signal intensity on T2 weighted images 	<ul style="list-style-type: none"> • hyperintense on T1- and T2-weighted images
Diagnosis	<ul style="list-style-type: none"> • Percutaneous fine needle aspiration (FNA) biopsy (CT or US guided) 	No FNA biopsy if ACC is suspected
Histopathological examination	B-cell NHL Diffuse large B-cell NHL Mixed small and large cell NHL Small cell NHL B-cell-lymphoma not specified T-cell-lymphoma NHL not specified Others Natural killer cell lymphoma Burkitt-like Lymphoma	Microscopic diagnostic score: Weiss score
Immunohistochemical examination	CD45 ⁺ (B & T-cell NHL) CD3 ⁺ /30 ⁺ /43 ⁺ /45RO ⁺ (T-cell NHL) CD20 ⁺ /40 ⁺ (B-cell NHL)	Ki-67 LI > 5 %
Therapy		
Treatment of choice	Chemotherapy	Open adrenalectomy
Alternative	Surgical debulking in combination with chemotherapy and/or radiation therapy	Mitotane (o,p'-DDD)
Adjuvant therapy	CNS prophylaxis	Chemotherapy in combination with mitotane
Outcome [median survival rate]	3,6 -34 months	18 months

was no evidence of malignancy, too. Histopathological examination of the left adrenal gland revealed a tumor with high mitotic rate and microscopic necrosis, but without clear evidence for malignancy according to histological criteria. The resection was classified as R0 (complete removal of tumor tissue). Therefore, no

adjuvant therapy was administered. The patient had an uneventful postoperative period and was discharged in good physical condition.

During the follow up (11 months after initial surgery) abdominal contrast-enhanced CT detected a tumor (3.7 × 5.5 cm) located in the splenorenal left

region with invasion in the adjacent organs. 2-[(18)F] fluoro-2-deoxyglucose (FDG)-PET scan was performed and showed an intense FDG accumulation in the left-sided tumor mass without abnormal FDG uptake in extraadrenal regions (Fig. 2B–C). Again, there was no evidence of metastatic disease. As adrenocortical carcinoma was suggested now, an open tumor resection including left nephrectomy, splenectomy and segmental resection of sigma was performed. Histological analysis confirmed the diagnosis of adrenocortical carcinoma and showed an infiltration of the tumor in adjacent organs (T4 N1 M0 R1, WHO stage IV). Therefore, the patient was administered adjuvant external tumor-bed radiation (total dose 50.4 Gy after 6 weeks) and adrenolytic medical treatment with high-dose mitotane.

After a five months period of clinical improvement the patient developed progression of ACC with disseminated intra-abdominal lymph node metastases. Because of infiltration of the left sided colon an open retroperitoneal tumor mass resection including sigmoidectomy and iliacal lymphonodectomy was performed. Adrenolytic treatment with mitotane was continued. Chemotherapy was denied by the patient. 23 months after primary diagnosis CT-scans of the abdomen showed further progression disease with disseminated peritoneal and intra-abdominal lymph node metastases (Fig. 2D–E). Again, palliative tumor resection and left-sided hemicolectomie were performed to avoid mechanic ileus. After reconvalescence, the patient was scheduled to receive polychemotherapy according to the FIRM-ACT study protocol (“First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment”; Etoposid, Doxorubicin, Cisplatin, Mitotane vs. Streptozotocin + Mitotane).

Discussion

The differential diagnosis of adrenal neoplastic disease includes primary tumors originating from the adrenal cortex or the adrenal medulla as well as metastases from primary carcinomas.

Benign non-hyperfunctioning adenomas comprise the majority of incidentally detected, asymptomatic adrenal masses [2, 4]. Hormonal activity increases with tumor size and mainly refers to production of cortisol (5–47%) or mineralocorticoids (1.6–3.3%). Benign tumors secreting sex hormones are rare [4]. Once

adrenal incidentalomas are discovered, their nature and endocrine function has to be defined to exclude hormonal dysfunction and malignancy.

Primary malignant tumors are adrenocortical carcinomas (ACC), primary adrenal lymphomas (PAL) and malignant pheochromocytomas. However, the incidence of these tumours is rather low [1–4]. Adrenal glands are more frequently the site of metastatic disease caused by primary carcinomas. In contrast to primary tumors, many metastases tend to invade both adrenal glands [1, 4, 10]. Although any primary cancer can spread to the adrenals, lymphoma, lung cancer, melanoma, leukaemia, kidney and ovarian carcinoma account for the majority of adrenal metastases [1, 4].

The incidence of adrenocortical carcinoma is estimated to be 0.4/100 000. It increases with tumor size to 25/100 000 (median diameter >6 cm) [4]. ACC accounts for about 0.02–0.2% cancer-related deaths and for up to 14% of adrenal incidentalomas. It shows a bimodal age distribution with peak incidence in first and fifth decades of life [1, 3, 4]. Indeed an exceptionally high annual incidence of ACC has been reported for children in southern Brazil and is probably related to a TP53 tumor suppressor gene mutation. Women are more often affected than men (ratio 1.5) [3, 11]. Bilateral manifestation is found in only 10% of the cases reported [1]. Average tumor size is mainly 11.5–12 cm (range: 2–36 cm), with only 4.2% tumors smaller than 6 cm [3, 11].

The molecular mechanisms of adrenocortical tumorigenesis are still not well understood. Recent studies assessing the differential gene expression patterns of benign and malignant adrenocortical tumors by cDNA macroarray allow to identify new tumor-suppressor genes and proto-oncogenes underlying adrenocortical tumorigenesis. Inactivating mutations at the 17p13 locus including the TP53 tumor suppressor gene and alterations of the 11p15 locus leading to IGF-2 overexpression are frequently observed. *In-vitro* experiments suggest that overexpressed IGF-2 acting via the IGF-1 receptor is relevant for adrenal cancer cell proliferation. Thus, the IGF-2 IGF-1 receptor pathway is a promising target for future therapies in ACC. Other results indicate that Chromogranin B and early growth response factor, 1HSP-60, Cyclin D1, jun proto-oncogene and topoisomerase I may play a role in ACC pathogenesis, too. In fact, larger series of patients are necessary to confirm the biologic, diagnostic, prognostic and therapeutic implications of these findings

[3, 12, 13].

PAL represents only 3% of extranodal lymphomas [1, 2, 5]. Secondary involvement of the adrenal gland with non-Hodgkin's lymphoma (NHL) is more frequent and occurs in nearly 25% of patients during the course of disease. PAL occurs with a male : female ratio of 3 : 1 and a median age of 68 years (range 39–89) [5, 7, 10]. In contrast to ACC, nearly 70% of PAL cases reveal a bilateral adrenal involvement with a median maximum diameter of 8 cm (range 4–17) at the time of diagnosis [7, 10]. Anyhow, considering the rather low incidence of PAL compared with the incidence of ACC and the fact that at least 10 % of all ACC cases show bilateral adrenal involvement every case with bilateral adrenal masses should be carefully evaluated for possible adrenocortical carcinoma. An accurate preoperative differentiation is absolutely necessary to ensure the correct treatment.

As human adrenal glands do not contain any lymphoid tissue, it is suggested that PAL arises from previous autoimmune adrenalitis. It seems to derive from haemopoietic tissue within a single adrenal gland and to gravitate to the microenvironment of the contralateral gland. This “homing theory” may partly explain bilateral disease and absence of nodal and marrow involvement by PAL [7, 9, 14]. Immune dysfunction seems to be the most important predisposing factor. According to a review of 55 patients with PAL by Wang *et al.* in 1998, 4% of patients suffered from human immunodeficiency virus (HIV) infection, 13% from concomittant autoimmune diseases, and 15% showed a past history of carcinoma [7, 15]. The data also implicates, that EBV may be a possible causative agent in the genesis of PAL. In addition, recent molecular analyses indicate that mutations of the p53 gene (53%) and the *c-kit* gene (71%) may play an additional role in adrenal lymphomagenesis [7, 15].

Clinical and laboratory findings

In contrast to our patient, many patients with ACC present with clinical symptoms of endocrine excess. Indeed, hormonally functioning tumors account for 26–94% of adrenocortical carcinomas [3, 4]. Rapid progressive hypercortisolism combined with virilisation due to androgen secretion in women is the most frequent symptom. High concentration of DHEA-S may suggest ACC, too, whereas decreased serum DHEA-S concentrations are more typical of a benign

adenoma. All in all, single secretion of estrogens, androgens or mineralcorticoides is rather rare. In many patients with a seemingly endocrine inactive ACC high concentrations of steroid precursors like androstenedione or 17 α -hydroxyprogesterone can often be demonstrated [3, 4]. In the absence of hormonal activity, early diagnosis is uncommon. Most patients with ACC are diagnosed at an advanced stage of disease with large primary tumors (median tumor size at diagnosis >10 cm) and an invasion in adjacent organs. Main clinical symptoms as abdominal discomfort (nausea, vomiting, abdominal fullness) or back pain are related to a mass effect of the large tumor. Remarkably, in patients with non-cortisol producing ACC well-being is often little affected, even in cases with large tumor size. Occasionally patients present with typical clinical tumor symptoms as fever, weight loss and anorexia [3, 4].

The clinical symptoms of PAL are quite variable and often related to the presence of lymphoma or adrenal insufficiency. PAL patients typically show a low incidence of extra-adrenal disease and an absence of leukaemia [5, 7, 10]. In 50% of these cases, an adrenal insufficiency is observed even when the neoplasms are small [5, 9, 10]. Skin pigmentation, gastrointestinal symptoms, profound fatigue, hypotension and Addison's disease have been mainly reported. Systemic symptoms as fever and weight loss as well as local lumbar pain have been described and could be found in our case as well. In some cases, rare symptoms including autoimmune haemolytic anaemia or thrombocytopenia, severe and diffuse skin itching, hypercalcaemia or unusual involvement of extranodal organs such as eye, thyroid gland, pituitary gland, or testicles can be found [7, 10, 16]. The incidence of CNS involvement is determined by the extent and proliferation of the disease. Risk factors include a high LDH serum level, a high/intermediate or high-risk International Prognostic Index (IPI) and the involvement of more than one extranodal site including bone marrow [7].

Radiological examinations

All adrenal tumors detected have to be diagnosed for their malignancy potential and hormonal activity to perform timely and curative treatment. Radiological, microscopic and macroscopic criteria have been established to differentiate between benign and malignant

lesion. However, none of these variables have proven entirely reliable.

Abdominal US largely depends on operator skills and tumor diameter [4, 5]. Whereas conventional US detects 65% of tumors <3 cm in diameter, endoscopic US may show even smaller lesions with a diameter of 1–2 cm [4]. However, US cannot be recommended for distinguishing between benign and malignant masses.

Contrast-enhanced CT is considered to be the most appropriate imaging tool to detect suspicious adrenocortical tumors and to differentiate between benign and malignant lesion [2, 4, 5, 17, 18]. Criteria of malignancy including inhomogeneity, irregularity of margins and irregular shape generally delivered a poor test performance [4, 5, 18]. Thus, both the tumour size and growth have been proposed to be important determinants to distinguish benign from malignant adrenal masses. However, attenuation thresholds have shown a better performance to diagnose adrenal malignancy than the tumour size or subjective criteria. In a review on 299 adrenalectomies Hamrahian *et al.* propose a non-contrast computed tomography attenuation value of 10 HU as a safe cut-off value to differentiate adenomas or hyperplasias from non-adenomas [18]. In cases with tumors of 4 cm or smaller, particularly in cases without a history of malignancy, 20 HU may be an acceptable cut-off value [4, 18]. However, a recent study including 151 adrenal masses with histologically confirmed diagnosis indicates an overlap between malignant and benign tumors and proposes delayed contrast-enhanced CT analyzing wash out of contrast medium for better discrimination of lipid-poor adenomas from ACC [3, 17]. In conclusion, adrenal lesions with an attenuation value of >10 HU in unenhanced CT or an enhancement washout of <50% and a delayed attenuation of >35 HU (on 10–15 min delayed enhanced CT) are suspicious for malignancy [3, 17].

As ACC and PAL are both malignant adrenal tumors they have a similar appearance on CT. Hence, the differentiation between both of them is difficult. The CT appearance of ACC is that of a large mass with central necrosis or calcification of the tumor in up to 30% of the cases. Enhancement is heterogeneous after administration of contrast medium. Venous extension of the tumor into the left vein or inferior vena cava as well as lymph node or other metastases (lung and liver) are common in advanced ACC and can usually be identified on contrast-enhanced images [1–4,

17–19]. In the majority of PAL cases, radiological appearance is not pathognomonic. CT demonstrates a complex mass with diffuse involvement of the gland and variable density of the lesion [1, 2, 5]. Whereas some cases appear as homogenous adrenal lesions, other cases exhibit cystic components due to areas of haemorrhage, cystic degeneration or necrosis. Enhancement after administration of intravascular contrast medium is less than that of the aorta or inferior vena cava [1, 2, 5].

In general chemical shift MRI does not provide additional information, but may be useful in ambiguous cases [4]. In contrast to benign tumours, malignant masses appear isointense to liver on T1-weighted images and hyperintense on T2 weighted images due to their higher fluid content. Additionally, malignant tumors show a strong contrast enhancement with delayed washout after injection of paramagnetic contrast [1–4, 17–19]. However, as MRI intensity mainly depends on the amount of intracytoplasmatic lipids inside the tumor, several exceptions may exist, *e.g.* with lipid-poor adenomas [4, 19]. On MRI, carcinomas are usually heterogeneously hyperintense on both T1- and T2-weighted images, reflecting the frequent internal haemorrhage and central necrosis. Enhancement is also heterogeneous, revealing nodular areas of intense enhancement and other areas with no enhancement. Washout of gadolinium enhancement is usually slow [2, 3]. On MRI, PAL usually shows low signal intensity on T1 and high signal intensity on T2 weighted images [2, 5].

In cases of radiographically indeterminate adrenal masses or past cancer history nuclear imaging is recommended for tumor diagnosis and selection of appropriate therapy. The main contribution of radionuclide imaging consists of functional information for tumor characterization. Since malignant tumors show an enhanced glycolytic metabolism with increased FDG uptake, PET is proposed for diagnosis, staging and detecting recurrences of adrenal malignomas. A differentiation between malignant and benign adrenal lesion can be performed using 18 FDG-PET with more than 95% accuracy [4, 19]. In particular, it plays an important role in evaluating treatment response and residual posttherapy masses. Several studies show a clear increase of FDG activity in malignant adrenal tumors, reflecting high glucose metabolism [4, 19, 20]. Moreover, PET imaging agents can also target specific adrenal gland enzymes expressed in tumor cells, inde-

pendent of secretory activity [19]. However, data are still insufficient to justify the application of FDG-PET for diagnosis of clinically inapparent masses outside clinical studies [4].

Adrenocortical scintigraphy achieves a relatively high sensitivity (71–100%) with a varying specificity (50–100%) to differentiate between benign and malignant adrenal masses [4, 20]. Today, the radiopharmaceuticals ¹²³I-MIBG and ¹³¹I-MIBG (metajodobenzylguanidine) and hydroxyephedrine are mainly used for the identification and localization of sympathomedullary diseases (medullar chromaffine tissue), including pheochromocytomas and extraadrenal paragangliomas. Thereby, the sensitivity of MIBG for detecting pheochromocytoma ranges between 80–90% with a specificity of 90–100% [4, 20].

¹³¹I-6 β -Iodomethylnorcholesterol (NP-59) scintigraphy is useful for detecting adrenocortical tumor tissue. It has a high specificity (100%) and reasonable sensitivity (70%) for distinguishing benign functioning adrenocortical adenomas from other adrenal lesions [20, 21]. Disadvantages of adrenal scintigraphy with iodocholesterol analogues are its restricted availability, time consuming procedure (3–5 days) and its association with relative high dosage of radiation. Thus, further larger studies are required to confirm the use of NP-59 scintigraphy for incidentally detected adrenal masses [20].

Recently, radiolabeled somatostatin analogs have been proposed in the diagnostic evaluation of several tumors. Malignant adrenal masses showed significant uptake of somatostatin analog, suggesting the presence of somatostatin receptors [20].

Angiographic findings are nonspecific and therefore not useful in diagnosis or follow-up of adrenal tumors [5]. In conclusion, preoperative differentiation between benign and malignant tumors is still the main problem in treatment of adrenal tumors.

Establishment of diagnosis

Percutaneous fine needle aspiration (FNA) biopsies under CT or US guidance can only be recommended in case of suspicious PAL or metastatic adrenal disease [4, 10, 22]. In the patient with PAL presented an early CT guided biopsy would have been indicated to avoid an in retrospect primary unnecessary operation. However, although its sensitivity to diagnose malignancy ranges between 81–100% with a specificity of 83–

100%, 6–50 % of the FNA biopsies are reported to be inconclusive [4]. Considering the risk of metastatic spread of cancer cells and the fact that a benign cytological diagnosis does not exclude malignancy, FNA cannot be approved as a standard procedure in the diagnostic workflow for suspicious adrenal masses [4]. Moreover, FNA should never be attempted before exclusion of pheochromocytoma by endocrine testing due to possible life-threatening hypertensive crises [4, 22].

Based on histopathological and immunophenotyping examinations, about 90% of PAL cases are B cell lymphomas. Only few reports describe T cell lymphomas with a suppressive or cytotoxic phenotype an expression of T-cell markers, *e.g.* CD 30, CD 43 and CD 45RO [5, 7–10, 15, 23–27]. The most common histology is the diffuse large-cell B cell lymphoma [5, 10], showing positive expressions of common leukocyte antigen CD 45 and of B-cell marker CD 20. Less common types are the small-cell lymphoma (11%, including cleaved-cell and non-cleaved-cell), the mixed small- and large-cell (9%) and the undifferentiated lymphoma [5, 7, 10]. Uncommon variants include anaplastic large-cell, angiotropic/intravascular or follicular grade I/II lymphoma [7, 28].

In our case of ACC, primary histological examination showed no clear evidence for malignancy. As the histopathological diagnosis of ACC is occasionally difficult (particularly with stage I and stage II disease), pathological examination should be performed by an experienced pathologist. The differentiation between benign and malignant adrenal lesions is based on macroscopic and microscopic features [3, 29]. For adrenocortical tumors the macroscopic classification system by Hough includes *e.g.* tumor weight >100 g, tumor cell necrosis, haemorrhage with vascular invasion or invasion of tumor capsule [30]. Hitherto, the Weiss score is the microscopic diagnostic score most widely used [31]. Nuclear atypia, atypical and frequent mitoses (>5/50 high power fields), eosinophilic tumor-cell cytoplasm (>75% of tumor cells), vascular and capsular invasion and necroses are suggestive for malignancy. Additionally, broad fibrous bands are a characteristic feature separating ACC from benign tumors [3, 31]. Nevertheless, there are still special types of ACC to which Weiss criteria are not fully applicable (*e.g.* pediatric adrenocortical tumors, oncozytomas, aldosterone-producing tumors of pure zona glomerulosa type) [30, 32]. Important additional in-

formation is gained from immunohistochemical staining. The immunohistochemical proliferation marker Ki-67 is a nuclear protein expressed by proliferating cells that can be observed in paraffin-embedded material using the primary antibody MIB 1. The percentage of Ki-67-positive tumor cells determines the tumor's proliferative activity. The Ki-67 labeling index or MIB1 (LI) is a simple and reproducible method in the differential diagnosis of adrenocortical tumors. Results of several studies using Ki-67 labeling index for differential diagnosis between adrenocortical adenoma and carcinoma suggest a strong correlation between Ki-67 expression and the malignancy of adrenocortical tumors in adults [33]. In the great majority of the cases, a Ki-67 LI greater than 5% separates benign lesions from adrenocortical carcinomas without overlap [34]. Moreover, Terzolo *et al.* observed that overall survival of patients with ACC was significantly reduced in case of high levels of the Ki-67 LI [35]. These findings suggest that the immunohistochemical marker Ki-67 may be of prognostic relevance concerning clinical outcome [36].

Other markers like D11, inhibin- α , melan A and chromogranin are helpful to define or exclude the adrenocortical origin of the tumor. Finally, several new markers (LOH at 17p13, IGF-2 overexpression, Cyclin E) have been proposed to separate benign from malignant adrenal lesions [3, 12]. Nevertheless, histopathological prognostic factors of ACC have not yet been fully established because of the rarity of the disease [30].

In the cases presented immunohistochemical analysis of the tissue resected showed an increased Ki-67 labeling index in case of adrenocortical carcinoma and CD45⁺ and CD20⁺ positive cells in case of primary adrenal lymphoma.

Treatment options

In general, surgery of adrenal tumors should be considered in patients with functioning cortical tumors and clinical symptoms [4, 37–39]. Regarding non-functioning tumors, recommendations for treatment mainly refer to the tumor size. In general, clinically inapparent lesions smaller than 3 cm without any criteria of malignancy are not resected and should be followed up closely by CT or MR scan every 6 or 12 months [4, 37–39]. Both, a close follow-up or adrenalectomy are reasonable treatment options for

intermediate sized tumours between 3 and 6 cm. In these cases, imaging should be repeated every 3 to 6 months to avoid misclassification of a small ACC as benign neoplasia [4, 37–39]. For lesions that do not increase in size, there are no data to support further radiological examination. Endocrine evaluation should be continued once a year for a period of 4 years [4]. In case of increase in tumor size or suspicion of malignancy, adrenalectomy should be strongly considered. Hitherto, adrenal lesion larger than 6 cm have been generally associated with a higher risk of malignancy and should have been removed [4, 17, 37–39], as performed in the cases presented.

Considering the surgical approach to adrenal tumors, minimally invasive adrenalectomy has proved to be a safe and reliable procedure for benign adrenal tumors with a diameter smaller than 6 cm. Many retrospective studies demonstrate its association with less intraoperative blood loss, lower postoperative morbidity, a shorter hospital stay, greater patients satisfaction and fewer incisional hernia [37–48]. At the moment still controversy exists about the appropriate surgical approach for tumors larger than 6 cm. Data suggest that at a size threshold of more than 4 cm, the likelihood of malignancy doubles (to 10%) and is more than nine fold higher for tumors larger than 8 cm (47%) [49]. However, in a recently published review on their experience with laparoscopic adrenalectomies Palazzo *et al.* have shown, that large size is not necessarily indicative of malignancy. Among 391 laparoscopic adrenalectomies performed, 19 solid cortical tumors were larger than 6 cm. Histological examination revealed adrenocortical carcinoma in only three cases [37].

Indications for an open adrenalectomy are a definitive or presumed diagnosis of primary adrenocortical carcinoma and circumstances technically obstructive to a minimally invasive approach. The maximum tumor size able to be successfully resected by LA is highly dependant on the skill of the surgeon [37–48]. Laparoscopic surgery performed for adrenal tumors >6 cm or for tumors that are preoperatively considered potentially malignant should be performed by an experienced laparoscopic surgeon. In case of any intraoperative features of malignancy conversion to an open approach should be performed in order to enable extensive radical compartmental resection [3, 37–50].

Surgical resection as a solitary treatment in patients with PAL is associated with a poor outcome [7]. Thus,

surgery has to be combined with additional therapeutic modalities including combination chemotherapy and/or radiation therapy and CNS prophylaxis [5, 7]. Surgical debulking of PAL in addition to chemotherapy may result in improved survival [7]. The regimes of chemotherapy comprise CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CHOP in combination with Rituximab, CHO (cyclophosphamide, doxorubicin, vincristine), CVP (vincristine, prednisone) or MACOP (cyclophosphamide, doxorubicin, prednisone, methotrexate, bleomycin). According to a review published by Kumar *et al.*, one third of the patients achieved a partial or complete remission during chemotherapy with a mean duration of survival of 34 ± 32 months [5]. Nevertheless, many PAL patients deceased due to tumour recurrence or severe infections within one year after diagnosis. In a recent review of 116 PAL cases between 1961 and 2006 we found information on primary treatment in 71 of the cases reported [unpublished data]. 47 (66%) of the patients received chemotherapy and 20 (28%) received surgery. Information on response on treatment and outcome was available in 102 (87.9%) patients. 64 (62.7%) patients had died, 22 (21.6%) patients showed complete and 16 (15.7%) patients showed partial remission. Mean overall-survival rate was 15.3 months. The role of radiation therapy on the adrenal gland is still unknown. The impact on long-term renal function when exposing both kidneys to irradiation and the likelihood of systemic spread of lymphoma cells generally precludes treatment with radiation alone or in combination with chemotherapy. Finally, CNS prophylaxis should be considered in cases with increased LDH serum levels and high or very high IPI score. Prophylactic intrathecal methotrexate and hydrocortisone applications may reduce the incidence of CNS recurrence and improve long-term survival in patients with aggressive NHL [7].

Hitherto, no significant advances in the treatment of adrenocortical carcinoma have been developed [3, 50]. In the absence of efficacious adjuvant therapy surgery remains the mainstay for primary and recurrent disease. Concerning the surgical approach open adrenalectomy is the procedure of choice in case of definitive or presumed diagnosis of ACC. In stages I–III resection including resection of invaded organs and lymphadenectomy reduces local recurrence rate and thus is associated with a prolonged disease free interval and long term patient survival rate [3, 11, 50–52]. To se-

cure optimal oncologic management and to decrease risk of tumor spillage and local recurrence avoiding capsular disruption is of utmost importance. Cobb *et al.* have reviewed the literature and identified 25 cases of ACC removed by laparoscopic resection [46]. Local recurrence or intraperitoneal dissemination occurred in 40% of patients. High local recurrence and peritoneal carcinomatosis after laparoscopic adrenalectomy was also observed in a recent series reported by Gonzalez *et al.* [41]. Incomplete resection of the primary tumor or metastatic disease not suitable to surgery is associated with a particular poor prognosis, too. Nevertheless, tumor debulking in cases of extended disease may help to control hormone excess and may facilitate other therapeutic options. Surgery for local recurrences or metastatic disease improves survival rates in retrospective studies [3, 47, 50].

Concerning adjuvant treatment for ACC, Mitotane (o,p'-DDD) has remained the only adrenal-specific agent available, showing modest effect concerning tumor regression in patients with unresectable, residual or metastatic disease. The percentage of significant tumor regression after Mitotane treatment varies between 25%–61% [3, 50, 53]. In the majority of patients additional control of hormone excess can be achieved. Mitotane has a specific cytotoxic effect on adrenocortical cells producing focal degeneration of the fascicular and particularly the reticular zone. Metabolic activation is essential for its adrenolytic activity. Mitotane has a narrow therapeutic window with adverse effects occurring in more than 80% of all patients [3, 50, 53]. Side effects are often dose limiting and mainly refer to gastrointestinal or central nervous system. Generally, they are reversible after cessation of mitotane. As mitotane induces adrenal insufficiency and increases the metabolic clearance of glucocorticoids, high-dose glucocorticoid replacement is needed during mitotane treatment. As not all patients respond to mitotane therapy, it is important to define the subset of patients likely to respond in order to avoid unnecessary treatment of patients [3, 50, 53]. Traditional cytotoxic chemotherapy for ACC has generally produced disappointing results, with only a minority of patients responding to current protocols. Cisplatin alone or in combination with etoposide seems to have some activity in ACC. As some in-vitro studies have indicated that mitotane may reverse multidrug—resistance and enhances tumor responsivity to cytotoxic drugs cytotoxic treatment may be combined with mitotane thera-

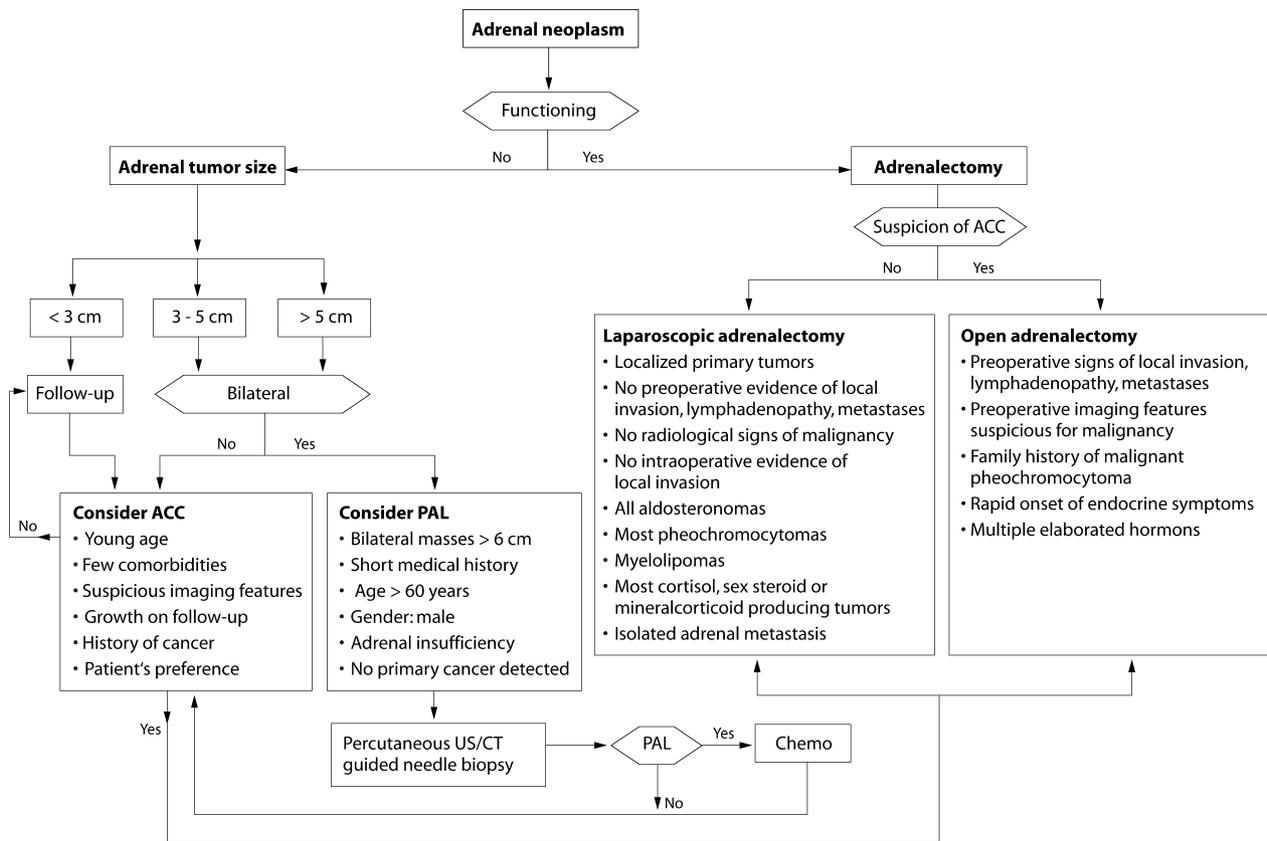


Fig. 3. Algorithm for diagnostic and therapeutic management of adrenal tumors.

py. Thus combination of mitotane with etoposide, doxorubicin, cisplatin or with streptozotocin have been proposed. Results differ concerning significant treatment toxicity and overall response rate (49% vs. 36%) [3]. Khan *et al.* recently reported a study on a second line cytotoxic chemotherapy regimen using a combination of vincristine, cisplatin, temiposide and cyclophosphamide (OPEC) after failure of streptozotocin plus mitotane in 11 patients. They observed a partial response in 2 patients and stable disease in seven patients with a median survival of 21 months after the start of OPEC [54]. The limited response to cytotoxic chemotherapy in ACC may be caused by high expression of the multidrug—resistance gene *mdr-1*. This results in high concentrations of p-glycoprotein acting as a drug efflux pump. Thus, antagonists of p-glycoprotein may improve the efficacy of cytotoxic therapy. [3, 55]. Regarding hormone excess adrenostatic drugs like ketoconazole, metyrapone, aminoglutethimide and etomidate may be used used to block steroidogenic enzymes and to lower circulating steroid hormones in the normal range [3].

Although radiotherapy has been often considered ineffective for treatment of ACC newer reports describe tumor response rates up to 42% and indicate, that ACC is not resistant to radiation therapy. Thus, radiation therapy is recommended to control localized disease in cases not amenable to surgery. Moreover, radiation therapy is the treatment of choice for most bone (and brain) metastases. Concerning adjuvant radiotherapy recent results demonstrate reduced local recurrence in patients with adjuvant radiotherapy of the tumor bed [3].

In order to summarize our therapeutic recommendations and to improve clinical differentiation between different primary malignant tumors of the adrenal gland we have extended the algorithms for surgical treatment of adrenal neoplasms published by Suzuki and Palazzo in 2006 [37, 39]. The approach presented in Fig. 3 includes clinical and radiological features suspicious of primary bilateral adrenal lymphoma and should help to establish diagnosis rapidly in order to start adequate therapy without any time delay.

Prognosis

In general, the prognosis of both tumor entities is poor. Adrenocortical carcinoma is associated with a short disease-free survival duration and a median survival rate of 18 months [4, 41]. While older studies suggested an improved outcome for functional tumors in adult patients, this results couldn't be confirmed in more recent studies [50]. Main problems in patients with localized, non-metastatic ACC are local recurrence or peritoneal carcinomatosis [4, 41]. Prognostic factors include tumor stage (I & II vs. III & IV), Weiss criteria (≤ 6 vs. > 6 criteria), mitotic index (≤ 20 vs.

> 20) and extent of surgery. Extensive surgical resection reduces local recurrence rate. Complete repeat resection of local recurrence improves survival rates, too [52].

Prognosis of patients with PAL is poor, too. In a recently published review by Kumar *et al.*, many PAL patients deceased due to tumor recurrence or severe infections within one year [5]. One third of the patients reviewed achieved a partial or complete remission during chemotherapy. The mean duration of survival in these patients was 34 ± 32 months, whereas the mean duration of survival in patients without response to chemotherapy was only 3.6 ± 3.9 months [5].

References

1. Lyon SM, Lee MJ (2002) Imaging the non-hyperfunctioning adrenal mass. *Imaging* 14: 137–146.
2. Dunnick NR, Korobkin M (2002) Imaging of adrenal incidentalomas: current status. *AJR American Journal Roentgenology* 179: 559–568.
3. Allolio B, Fassnacht M (2006) Clinical review: Adrenocortical Carcinoma: Clinical Update. *Journal of Clinical Endocrinology and Metabolism* 91: 2027–2037.
4. Mansmann G, Lau J, Balk E, *et al.* (2004) The clinically inapparent adrenal mass: update in diagnosis and management. *Endocrine Reviews* 25: 309–340.
5. Kumar R, Xiu Y, Mavi A, *et al.* (2005) FDG-PET imaging in primary bilateral adrenal lymphoma: a case report and review of the literature. *Clinical Nuclear Medicine* 30: 222–230.
6. Mantzios G, Tsirigotis P, Veliou F, *et al.* (2004) Primary adrenal lymphoma presenting as Addison's disease: case report and review of the literature. *Annals of Hematology* 83: 460–463.
7. Grigg AP, Connors JM (2003) Primary adrenal lymphoma. *Clinical Lymphoma* 4: 154–160.
8. Fukushima A, Okada Y, Tanikawa T, *et al.* (2003) Primary bilateral adrenal intravascular large B-cell lymphoma associated with adrenal failure. *Internal Medicine* 42: 609–614.
9. Zargar A, Laway B, Bhat K, *et al.* (2004) Adrenal insufficiency due to primary bilateral adrenal non-Hodgkin's lymphoma. *Experimental and Clinical Endocrinology and Diabetes* 112: 462–464.
10. Tumino S, Leotta ML, Branciforte G, *et al.* (2003) Bilateral adrenal non-Hodgkin lymphoma type B. *Journal of Endocrinological Investigation* 26: 1120–1123.
11. Kebebew E, Reiff E, Duh QY, *et al.* (2006) Extent of disease at presentation and outcome for adrenocortical carcinoma: have we made progress? *World Journal of Surgery* 30: 872–878.
12. Lombardi CP, Raffaelli M, Pani G, *et al.* (2006) Gene expression profiling of adrenal cortical tumors by cDNA macroarray analysis. Results of a preliminary study. *Biomedicine and Pharmacotherapy* 60: 189–190.
13. Slater E, Diehl S, Langer P, *et al.* (2006) Analysis by cDNA microarray of gene expression patterns of human adrenocortical tumors. *European Journal of Endocrinology* 154: 587–598.
14. Ellis, RD, Read D (2000) Bilateral non-Hodgkin's lymphoma with adrenal insufficiency. *Postgraduate Medical Journal* 76: 508–509.
15. Wang J, Sun NCJ, Renslo R, *et al.* (1998) Clinical silent primary adrenal lymphoma: A case report and review of the literature. *American Journal of Hematology* 58: 130–136.
16. Terpos E, Theocharis S, Panitsas F, *et al.* (2004) Autoimmune hemolytic anemia with myelodysplastic features followed by bilateral adrenal non-hodgkin lymphoma: a case report and review of the literature. *Leukemia and Lymphoma* 45: 2333–2338.
17. Fassnacht M, Kenn W, Allolio B (2004) Adrenal tumors: how to establish malignancy? *Journal of Endocrinological Investigation* 27: 387–399.
18. Hamrahian AH, Ioachimescu AG, Remer EM, *et al.* (2005) Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. *Journal of Clinical Endocrinology and Metabolism* 90: 871–877.
19. Pacak K, Eisenhofer G, Goldstein DS (2004) Functional imaging of endocrine tumors: role of positron emission tomography. *Endocrine Reviews* 25: 568–580.
20. Maurea S, Klain M, Mainolfi C, *et al.* (2001) The diag-

- nostic role of radionuclide imaging in evaluation of patients with nonhypersecreting adrenal masses. *Journal of Nuclear Medicine* 42: 884–892.
21. Imperiale A, Olianti C, Manelli M, *et al.* (2005) Tomographic evaluation of ¹³¹I-6 β -Iodomethyl-norcholesterol standardised uptake trend in clinically silent monolateral and bilateral adrenocortical incidentalomas. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging* 49: 287–296.
 22. Nurnberg D (2005) Ultrasound of adrenal gland tumors and indications for fine needle biopsy. *Ultraschall in der Medizin* 26: 458–469.
 23. Levy NT, Young WF, Habermann TM, *et al.* (1997) Adrenal insufficiency as a manifestation of disseminated non-Hodgkin's lymphoma. *Mayo Clinic Proceedings* 72: 818–822.
 24. Pimentel M, Johnston J, Allan D, *et al.* (1997) Primary adrenal lymphoma associated with adrenal insufficiency: a distinct clinical entity. *Leukemia and Lymphoma* 24: 363–367.
 25. Xu A, Xiao X, Ye L, *et al.* (2003) Primary adrenal lymphoma. *Leukemia and Lymphoma* 44: 739–740.
 26. Tsai W, Hsieh C, Cheng M, Lin CK (2006) Adrenal insufficiency in T-cell lymphoma. *International Journal of Urology* 13: 794–797.
 27. May F, Bachor R, Hack M, *et al.* (1998) Primary adrenal non-Hodgkin's lymphoma: long-term survival. *Journal of Urology* 160: 487.
 28. Frankel WL, Shapiro P, Weidner N (2000) Primary anaplastic large cell lymphoma of the adrenal gland. *Annals of Diagnostic Pathology* 4: 158–164.
 29. Aiba M, Fujibayashi M (2005) Histopathological diagnosis and prognostic factors in adrenocortical carcinoma. *Endocrine Pathology* 16: 13–22.
 30. Hough A, Hollifield J, Page D (1979) Prognostic factors in adrenal cortical tumors. *American Journal of Clinical Pathology* 72: 390–399
 31. Weiss LM (1984) Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *American Journal of Surgical Pathology* 8: 163–169.
 32. Pohlink C, Tannapfe A, Eichfeld U, *et al.* (2004) Does tumor heterogeneity limit the use of the Weiss criteria in the evaluation of adrenocortical tumors? *Journal of Endocrinological Investigation* 27: 565–569.
 33. Goldblum JR, Shannon R, Kaldjian EP, *et al.* (1993) Immunohistochemical assessment of proliferative activity in adrenocortical neoplasms. *Mod Pathol* 6: 663–668.
 34. Wachenfeld C, Beuschlein F, Zwermann O (2001) Discerning malignancy in adrenocortical tumors: are molecular markers useful? *Eur J Endocrinol* 145: 335–341.
 35. Terzolo M, Boccuzzi A, Bovio S (2001) Immunohistochemical assessment of Ki-67 in the differential diagnosis of adrenocortical tumors. *Urology* 57: 176–182.
 36. Sasano H, Imatani A, Shizawa S, *et al.* (1995) Cell proliferation and apoptosis in normal and pathologic human adrenal. *Mod Pathol* 8: 11–17.
 37. Palazzo FF, Sebag F, Sierra M, *et al.* (2006) Long-term outcome following laparoscopic adrenalectomy for large solid adrenal cortex tumors. *World Journal of Surgery* 30: 893–898.
 38. Valeri A, Bergamini C, Manca G, *et al.* (2005) Adrenal Incidentaloma: The influence of a decision-making algorithm on the short-term outcome of laparoscopy. *Journal of Laparoendoscopic and Advanced Surgical Techniques* 15: 451–459.
 39. Suzuki H (2006) Laparoscopic adrenalectomy for adrenal carcinoma and metastases. *Current Opinion in Urology* 16: 47–53.
 40. Sturgeon C, Kebebew E (2004) Laparoscopic adrenalectomy for malignancy. *The Surgical Clinics of North America* 84: 755–774.
 41. Gonzalez RJ, Shapiro S, Sarlis N, *et al.* (2005) Laparoscopic resection of adrenal cortical carcinoma: A cautionary note. *Surgery* 138: 1078–1086.
 42. MacGillivray D, Whalen G, Malchoff C, *et al.* (2002) Laparoscopic resection of large adrenal tumors. *Annals of Surgical Oncology* 9: 480–485.
 43. Lombardi CP, Raffaelli M, De Crea C, Bellantone R (2006) Role of laparoscopy in the management of adrenal malignancies. *Journal of Surgical Oncology* 94: 128–131.
 44. Gagner M, Lacroix A, Bolte E (1992) Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *New England Journal of Medicine* 327: 1033.
 45. Porpiglia F, Fiori C, Tarabuzzi R, *et al.* (2004) Is laparoscopic adrenalectomy feasible for adrenocortical carcinoma or metastasis? *BJU International* 94: 1026–1029.
 46. Cobb WS, Kercher KW, Sing RF, Heniford BT (2005) Laparoscopic adrenalectomy for malignancy. *Journal of American Surgery* 189: 405–411.
 47. Tsuru N, Ushiyama T, Suzuki K (2005) Laparoscopic adrenalectomy for primary and secondary malignant adrenal tumors. *Journal of Endourology* 19: 702–709.
 48. Walz MK, Petersenn S, Koch JA, *et al.* (2005) Endoscopic treatment of large primary adrenal tumours. *British Journal of Surgery* 92: 719–723.
 49. Sturgeon C, Shen WT, Clark OH, Duh OY, 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: 423–430.
 50. Roman S (2006) Adrenocortical carcinoma. *Current Opinion in Oncology* 18: 36–42.
 51. Schulick R, Brennan M (1999) Long-term survival

- after complete resection and repeat resection in patients with adrenocortical carcinoma. *Annals of Surgical Oncology* 17: 26–34.
52. Causeret S, Monneuse O, Mabrut J, *et al.* (2002) [Adrenocortical carcinoma: prognostic factors for local recurrence and indications for reoperation. A report on a series of 22 patients]. *Annales de Chirurgie* 127: 370–377.
 53. Hahner S, Fassnacht M (2005) Mitotane for adrenocortical carcinoma treatment. *Current Opin in Investigational Drugs* 6(14): 2407–2417.
 54. Khan TS, Sundin A, Juhlin C, *et al.* (2004) Vincristine, cisplatin, teniposide, and cyclophosphamide combination in the treatment of recurrent or metastatic adrenocortical cancer. *Medical Oncology* 21: 167–177.
 55. Kirschner L (2006) Emerging treatment strategies for adrenocortical carcinoma: a new hope. *Journal of Clinical Endocrinology and Metabolism* 91: 14–21.