Langenbeck's Archives of Surgery (2019) 404:385–401
https://doi.org/10.1007/s00423-019-01768-z

SYSTEMATIC REVIEWS AND META-ANALYSIS

Surgical therapy of adrenal tumors: guidelines from the German Association of Endocrine Surgeons (CAEK)

K. Lorenz[1] · P. Langer[2] · B. Niederle[3] · P. Alesina[4] · K. Holzer[5] · Ch. Nies[6] · Th. Musholt[7] · P. E. Goretzki[8] · N. Rayes[9] · M. Quinkler[10] · J. Waldmann[11] · D. Simon[12] · A. Trupka[13] · R. Ladurner[14] · K. Hallfeldt[14] · A. Zielke[15] · D. Saeger[16] · Th. Pöppel[17] · G. Kukuk[18] · A. Hötker[19] · P. Schabram[20] · S. Schopf[21] · C. Dotzenrath[22] · P. Riss[23] · Th. Steinmüller[24] · I. Kopp[25] · C. Vorländer[26] · M. K. Walz[4] · D. K. Bartsch[5]

Received: 14 February 2019 / Accepted: 19 February 2019 / Published online: 1 April 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Background and aims Previous guidelines addressing surgery of adrenal tumors required actualization in adaption of developments in the area. The present guideline aims to provide practical and qualified recommendations on an evidence-based level reviewing the prevalent literature for the surgical therapy of adrenal tumors referring to patients of all age groups in operative medicine who require adrenal surgery. It primarily addresses general and visceral surgeons but offers information for all medical doctors related to conservative, ambulatory or inpatient care, rehabilitation, and general practice as well as pediatrics. It extends to interested patients to improve the knowledge and participation in the decision-making process regarding indications and methods of management of adrenal tumors. Furthermore, it provides effective medical options for the surgical treatment of adrenal lesions and balances positive and negative effects. Specific clinical questions addressed refer to indication, diagnostic procedures, effective therapeutic alternatives to surgery, type and extent of surgery, and postoperative management and follow-up regime.

Methods A PubMed research using specific key words identified literature to be considered and was evaluated for evidence previous to a formal Delphi decision process that finalized consented recommendations in a multidisciplinary setting.

Results Overall, 12 general and 52 specific recommendations regarding surgery for adrenal tumors were generated and complementary comments provided.

Conclusion Effective and balanced medical options for the surgical treatment of adrenal tumors are provided on evidence-base. Specific clinical questions regarding indication, diagnostic procedures, alternatives to and type as well as extent of surgery for adrenal tumors including postoperative management are addressed.

✉ K. Lorenz
kerstin.lorenz@uk-halle.de

[1] Universitätsklinikum Halle, Halle/Saale, Germany
[2] Klinikum Hanau, Hanau, Germany
[3] Ordination Siebenbrunnenstrasse, Wien, Austria
[4] Kliniken Essen-Mitte, Essen, Germany
[5] Universitätsklinikum Marburg, Marburg, Germany
[6] Marienhospital Osnabrück, Osnabrück, Germany
[7] Universitatsklinikum Mainz, Mainz, Germany
[8] Charité Universitätsmedizin Berlin, Berlin, Germany
[9] Universitätsklinikum Leipzig, Leipzig, Germany
[10] Endokrinologiepraxis Berlin, Berlin, Germany
[11] MIVENDO Klinik Hamburg, Hamburg, Germany
[12] Evangelisches Krankenhaus BETHESDA Duisburg, Duisburg, Germany
[13] Klinikum Starnberg, Klinikum Starnberg, Germany
[14] Ludwig-Maximilians-Universität München, München, Germany
[15] Diakonie-Klinikum Stuttgart, Stuttgart, Germany
[16] Universitätsklinikum Hamburg, Hamburg, Germany
[17] Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany
[18] Universitätsklinikum Bonn, Bonn, Germany
[19] Universitätsklinikum Zürich, Zürich, Switzerland
[20] RAE Ratacjzak und Partner, Sindelfingen, Germany
[21] Krankenhaus Agatharied, Hausham, Germany
[22] HELIOS Universitätsklinikum Wuppertal, Wuppertal, Germany
[23] Medizinische Universität Wien, Wien, Austria
[24] Deutsches Rotes Kreuz Krankenhaus Berlin, Berlin, Germany
[25] AWMF, Frankfurt am Main, Germany
[26] Bürgerhospital Frankfurt, Frankfurt am Main, Germany

Keywords Adrenal surgery · Guideline · Conn syndrome · Pheochromocytoma · Adrenal Cushing disease

Introduction

The aim of the present guideline was to provide practical and qualified recommendations on an evidence-based level reviewing the prevalent literature for the surgical therapy of adrenal tumors. The full-text version in German language is available online (awmf.org/leitlinien/detail/ll/088-008.html) [1]. Six medical societies and organizations as well as a patient support group collectively actualized previous recommendations (04/2000) and subsumed a joint S2k guideline [2].

This guideline refers to patients of all age groups in operative medicine who require adrenal surgery. It primarily addresses general and visceral surgeons but offers information for all medical doctors related to conservative, ambulatory or inpatient care, rehabilitation, and general practice as well as pediatrics. The guideline extends to interested patients with the aim to improve the knowledge and participation in the decision-making process regarding indications and methods of management of adrenal tumors.

The aim of the guideline is to provide preferably the most effective medical options for the surgical treatment of adrenal lesions. Positive and negative effects balance medical effectiveness while aspects of efficiency and economics are secondarily considered. Moreover, organizational and legal aspects are observed.

The guideline specifically addresses the following questions:

- What are the indications for surgery in adrenal tumors?
- What diagnostic measures are required preoperatively?
- Do effective alternative therapy options to surgery exist?
- What kind of procedures of adrenal resection should be performed?
- What measures are required in the postoperative care?

Methods

This guideline represents an update of the S1 guideline passed 4/2000 "surgical therapy of adrenal diseases" (CAEK; Mitteilungen der Deutschen Gesellschaft für Chirurgie, G92) [1]. In accordance with the requirements of S2 guidelines of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) classification and regulations (http://www.awmf-leitlinien.de) as well as the German instrument for methodical guideline assessment of the AWMF and ÄZQ (DELBI, http://www.delbi.de), the previous recommendations underwent thorough survey and revision on base of a systematic literature review.

Following the mandation process by the members of the German Association of Endocrine Surgeons, leading coordinators convened multidiciplinary experts, legal guidance, and patient support groups. The project was registered online on November 14, 2017 at the AWMF (www.awmf-leitlinien.de, AWMF-Registernummer 088-008) and publicly announced to enable participation or comments. Representativeness of the mandated members was reviewed and confirmed by the 11 working groups who composed a manuscript that underwent written Delphi voting on January 1, 2018. Comments were incorporated by the coordinators (KL, DKB) and underwent written Delphi voting, which was followed by a consensus conference on June 6, 2018 in Frankfurt/Main for final live voting process, moderated by an AWMF representative. A list of the entire constituting members, represented medical societies, and organizations of the guideline group is presented in Appendix.

Phrasing of the recommendations and consensus process

Based on the previous S1 guideline surgical therapy of adrenal diseases published 2000 (Mitteilungen der Deutschen Gesellschaft für Chirurgie, G92) [2], a literature review was performed, and the actualised S2k guidelines generated [1]. A PubMed research using the key words "guidelines" AND "adrenal tumor" AND "surgery"; "adrenal tumor" AND "surgery"; "Conn adenoma" AND "surgery"; "pheochromocytoma" AND "surgery"; "adrenal incidentaloma" AND "surgery"; "adrenocortical carcinoma" AND "surgery"; "adrenal myelolipoma" AND "surgery"; "adrenalectomy" AND "perioperative management" for the interval January 2000–June 2016 was performed, and identified publications were analyzed in the assigned working groups. Of these, only few studies represent evidence-based data, and the majority are retrospective analyses (evidence level III), randomized prospective trials are exceptional (evidence level I and II). Currently, only the American Association of Clinical Endocrinologists (AACE) and the European Network for the Study of Adrenal Tumors (ENSAT) present valid recommendations for incidental adrenal tumors based on systematic literature review with evaluation of evidence levels. The new S2k guideline was generated in accordance with recommendations from the Study of Adrenal Tumors (ENSAT), the European Society of Endocrine Surgeons (ESES), the American Association of

Clinical Endocrinologists (AACE), the Associazione Medici Endocrinologi, the European Society of Endocrinology (ESE), and the British Endocrine Association, data from published meta-reviews, and original published data. All studies that were consulted for generation of this guideline are gathered in the reference list.

In presentation of the substance, it was distinguished between core statements/key recommendations and the generation from and presentation in the primary literature (evidence level). Recommendations discriminate quality levels of strength by wording (e.g., "has to"/"must"; "should"; "can"). Recommendations *against* an intervention are phrased accordingly. In general, the level of recommendation is determined by the quality of evidence (evidence power); thus, a recommendation of average evidence level corresponds to an average recommendation grade. Consensus level was graded with high consensus (> 95% approval, +++), consensus (> 75–95% approval, ++), or majority consensus (50–75% approval, +) in accordance with classification in the AWMF regulations. All recommendations were passed with high consenus or consensus.

Consensus procedure

Eleven working groups were initiated to actualise and overwork the areas of general recommendations, non-functional adrenal tumors, primary hypercortisolism, androgene-/estrogene-producing tumors, primary hyperaldosteronism, pheochromocytoma and paraganglioma, neuroblastoma, ganglioneuroblastoma, ganglioneuroma, adrenal carcinoma, adrenal metastases, peri-, and postoperative management and care. The primary version was circulated to all members. Comments and alternative votes for all statements and recommendations of all members were collected by the coordinators, and consensus phrasing was perfomed in alignement. Preelection of these was done in a written Delphi process, after which all members of the guideline group and all medical societies were invited to comment and provide alternative proprosals. In a concluding consensus conference, involving all members of the guideline group, the representatives of the medical societies reviewed each statement. Moderated by a neutral AWMF representative, each statement and recommendation was seperately discussed and voted, allowing for questions, recording, and collection of modifications of all reasonable changes, and finalizing voting of the modified phrasing by the moderator (nominal group process). Open voting for each single recommendation during the live consensus conference was performed following final editing of statement and recommendation phrasing. Voting rates for approval and disapproval were registered for each recommendation separately. Objections and proposal for modifications were registered and finally addressed in a novel voting process. All recommendations were approved with strong consensus (approval of > 95% of members) or in consensus (approval of > 75% of members). Afterwards, a final editing of the consented commentaries to each recommendation was performed by the working groups and summarized by the coordinators (KL, DKB). The manuscript was then circulated for final approval to all medical societies involved and presented to the board committee of the DGAV (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie) with option to comment and provide alternative proposals. The consented recommendations were thereby left unchanged.

General recommendations for surgery

R1: Functional adrenal tumors generally represent an indication for surgery irrespective of their size (consensus+++).

R2: In a given indication for surgery, primary adrenal tumors ≤ 6 cm without signs of malignancy should be operated minimally invasively (consensus+++).

R3: Laparoscopic and retroperitoneoscopic approaches are equal. The choice depends on experience and preference of the surgeon (consensus+++).

R4: Non-functional adrenal tumors (exception myelolipoma) with diameter ≥ 6 cm should be operated in open technique due to the risk of malignancy.

In tumors from 4 to 6 cm, indication for surgery is to be decided on individual patient criteria.

Non-functional adrenal tumors < 4 cm without criteria of malignancy should not be operated. Indication for surgery should be decided interdisciplinary (consensus+++).

R5: In open adrenalectomy, transabdominal or thoracoabdominal approaches are preferred as suspicion of malignancy and large tumor size is the main indication for these approaches (consensus+++).

R6: "Single-port" and "multiple-port" adrenalectomy are equal. Utilization of a robot in minimally invasive adrenalectomy demonstrated as yet no advantage (consensus+++).

R7: Standard procedure for unilateral tumors is adrenalectomy. Adrenal preserving resection may be considered in case all functional tissue can be completely removed (consensus+++).

R8: For bilateral adrenal tumors, preservation of adrenocortical functional reserve is to be pursued. Minimum of one third of adrenal tissue is therefore required; preservation of the adrenal vein is not obligatory (consensus+++).

R9: There is no indication for surgery in asymptomatic myelolipoma and asymptomatic adrenal cyst. Due to their benign nature, tumor diameter is not relevant (consensus+++).

R10: Adrenocortical carcinoma requires open surgery. In tumors < 6 cm without signs of local or lymph node infiltration (ENSAT stage I + II), minimally invasive adrenalectomy can be performed in given expertise (consensus+++).

Adrenocortical carcinoma without evidence of distant metastases requires radical tumor resection without capsular

rupture and locoregional lymphadenectomy. Indication for resection of tumors with oligo metastases should be based on individual assessment (consensus+++).

R11: Bilateral adrenalectomy may represent an ultima ratio in ACTH-dependent Cushing's syndrome when causative therapy fails (consensus+++).

R12: Indication for resection of adrenal metastases should be made on patients' individual criteria (consensus+++).

Resection of adrenal metastases can be performed minimally invasive. In case of tumor size > 6 cm or signs of infiltration of neighboring structures, surgery should be performed in open technique (consensus++).

Commentary

Exception to R1 is primary hyperaldosteronism due to bilateral hyperplasia without reliable definition of right or left origin.

Limits for a minimally invasive approach are tumor size and imaging criteria of malignancy. Regarding size, a 6-cm rule is accepted, larger tumors may be approached conventionally open; however, in lack of evidence for this rule, in exceptional expertise, larger tumors may be also approached minimally invasively if the patient is informed and a complete excision can safely be performed without capsular rupture [3–5].

Tumor size and imaging morphology determine the indication for surgery. There is evidence for a positive correlation of tumor size and risk of malignancy [6, 7]. Prevalent data suggest increasing risk of malignancy in tumors > 4 cm, arguing for the indication for surgery, ideally after interdisciplinary consultation [8]. Imaging criteria for malignancy remain uncertain unless infiltrations of neighboring structures or metastases are prevalent. Additional information with Houndsfield units (HU) > 10 in native CT or MRI with chemical shift imaging may provide further guidance [9, 10].

In due consideration of the risk of malignancy in tumors > 6 cm and imaging criteria for malignancy with general recommendation for open surgery, some clinical data support laparoscopic approach in adrenocortical carcinoma and larger tumors or show equal outcomes regarding recurrence and prognosis. Therefore, providing great experience and dedicated patients' informed consent, a minimally invasive approach for tumors up to 10 cm may be eligible in individual patients [11, 12].

Adrenalectomy is the standard procedure for all adrenal tumors with indication to surgery; however, preservation of the adrenocortical functional reserve, requiring about a third of the non-tumorous remnant of the adrenal, is increasingly acknowledged and may be indicated especially in Conn syndrome with small tumors, rarely in Cushing adenoma. For this, preservation of the adrenal vein is not obligatory [13–16].

Ideal indications for adrenal preserving surgery are hereditary disease, namely bilateral pheochromocytoma, and Cushing's syndrome with bilateral macronodular hyperplasia as typical complications of corticoid substitution therapy may be avoided [14, 17, 18]. This advantage needs to be weighed against the risk of local tumor recurrence in the adrenal remnant. Clinical data indicate a higher incidence of hereditary pheochromocytoma up to 19% as previously estimated. Although risk factors remain unreliable, age < 45 years, extraadrenal tumor localisation, previous cervical paraganglioma, and multiple tumors were identified in multivariate analysis and should be acknowledged [19]. Substitution-free survival is also described in adrenal preserving surgery for Cushing's syndrome [20].

Decision on the optimal approach in suspicion of adrenocortical cancer (laparoscopic vs. open) should regard the individual risk of tumor capsule rupture and incomplete resection, and demands appropriate surgical expertise. Open adrenalectomy remains the standard therapy for tumors > 6 cm and evidence of infiltration. Incidence of lymph node infiltration in adrenal adrenocortical cancer is about 20%; however, the role of lymphadenectomy remains undefined in regard to outcome and locoregional extension [18–20].

Curative trans-sphenoidal tumor resection remains standard therapy for ACTH-dependent Cushing's syndrome; however, in up to 31% incomplete tumor resection and recurrence demand further neurosurgery or radiation [21]. In failure of these measures or in case of paraneoplastic excess cortisol expression, bilateral adrenalectomy may provide efficient improvement of clinical symptoms with minimum recurrence rate [22].

Criteria in favor for adrenalectomy as a treatment option of adrenal metastases are control of extraadrenal tumor manifestation and patients' general health performance status in regard of planned adrenal surgery. Biopsy confirmation is unnecessary when imaging and patients' history are confirmative [23]. While some tumor entities demonstrate advantages of adrenalectomy in metastasis, a poorer prognosis is associated with a period of < 2 years of primary malignant diagnosis and evidence of adrenal metastasis, further distant metastases, or incomplete adrenal tumor resection [24]. Adrenalectomy may also be offered in palliative intention, e.g., for control of otherwise refractory pain. Minimally invasive surgery shows equal results to open surgery and may be offered in given expertise [25]; however, open surgery remains the standard approach when multivisceral resection is required. In case adrenalectomy is judged unfavorable, radiofrequency ablation (RFA) may be considered [26].

Primary hyperaldosteronism

R13: The primary hyperaldosteronism (PHA) has to be established preoperatively, e.g., by determination of the aldosterone-renin-quotient (ARQ) (consensus+++).

R14: A lateralization of the disease has to be preoperatively established by imaging and regional localization procedures since the results influence the indication for the operation and the operative strategy (consensus+++).

A cross-sectional imaging has to be performed preoperatively with contrast enhanced computer tomography or MRI imaging. In addition, an endosonography can be performed (consensus+++).

In case of unclear lateralization by imaging, an adrenal venous sampling (AVS) should be performed preoperatively for the functional lateralization of the PHA. In case of clear lateralization by cross-section imaging, the AVS can be omitted if the patient was informed in detail about the risk of a resection of a hormonally inactive lesion. An AVS should not be performed in patients < 40 years with established PHA, a clear unilateral tumor, and a normal contralateral adrenal on imaging (consensus+++).

R15: An adrenal scintigraphy can be performed in case of inconclusive lateralization by AVS (consensus+++).

R16: In the unilateral form of PHA, an operation has to be indicated (consensus+++).

R17: In patients with PHA and bilateral adrenal lesions, an operation can be considered if the AVS shows a functional lateralization (consensus+++).

R18: In patients with PHA and hyperplasia of the adrenal cortex without clear lateralization in the AVS, an operation should not be indicated (consensus+++).

R19: The adrenalectomy should be performed minimally invasive (consensus+++).

R20: In case of a solitary aldosterone producing adenoma (APA), a partial resection of the affected adrenal gland can be performed (consensus+++).

Commentary

The primary hyperaldosteronism (PHA) is caused by an autonomous aldosterone secretion. The determination of the aldosterone–renin quotient (ARQ) allows the identification of patients even with a mild form PHA [27, 28]. The ARQ test is an excellent screening test in the diagnosis of PHA. Patients with an abnormal ARQ should undergo a confirmatory test. The most frequently used confirmatory test is the intravenous NaCl-stress test [29]. Cross-sectional imaging and functional lateralization of the increased aldosterone production is essential for the indication for surgery and for the operative strategy, since only patients with a clearly localized PHA to one adrenal should undergo surgery. CT is the standard cross-sectional imaging method for the imaging of a PHA. However, the identification of a small adenoma can be difficult, since most aldosterone-producing adenomas (APA) are less than 2 cm in size, and the functionality of any detected lesion cannot be established. MRI imaging can be used alternatively to CT imaging. The endoscopic ultrasound of the adrenals can be very useful for the morphological detection of a small adrenal adenoma [30–32]. The adrenal venous sampling (AVS) allows the functional lateralization of the PHA [33]. However, the result of the AVS is highly dependent on the experience of the examiner; especially, the cannulation of the right adrenal vein is difficult and has a success rate of at most 75% [34, 35]. Thus, the principal use of the AVS is discussed controversially. In case of a clear lateralization of the APA, especially in younger patients < 40 years, the primary surgery is justified without AVS, if the patient agrees after detailed information about the risk of an inadequate operation. In case of an unclear lateralization by imaging, the AVS is recommended to avoid the risk of an unnecessary or inadequate adrenalectomy [36–38]. The adrenal scintigraphy with iodine 131-norcholesterol (NP-59) in association with dexamethasone suppression test is also an opportunity for functional lateralization. However, in adenomas < 1.5 cm in size, the uptake of the tracer is too low in most cases to functionally characterize small adrenal lesions detected by CT [39].

Patients with a PHA clearly associated with one adrenal (unilateral form of PHA) benefit from adrenalectomy [40–42]. One important aspect is that surgery reduces not only the pathophysiologically negative effect of the increased aldosterone production on hypertension but also with regard to the fibrosis of the myocard and endothelia [43, 44]. With regard to these aspects, surgery is much more effective than medical treatment with, e.g., spironolactone [43, 45]. In contrast, no surgery should be indicated in patients with PHA and hyperplasia of the adrenal cortex without unequivocal lateralization in the AVS. In case of bilateral adrenal hyperplasia, patients do not benefit from an operation, since unilateral adrenalectomy only marginally influences the increased aldosterone production. Bilateral adrenalectomy is not justified, because of the consecutive need of daily glucocorticoid substitution. In bilateral adrenal hyperplasia of the adrenal cortex, surgery can be indicated, if the AVS clearly shows lateralization to one adrenal gland. Furthermore, in case of asymmetric hyperplasia of the adrenal cortex, the patient might benefit from resection of the dominant adrenal [46]. The minimally invasive adrenalectomy is nowadays the procedure of choice in PHA, which can be performed by either a transperitoneal or retroperitoneal approach [47, 48]. A conventional approach should be restricted to exceptional situations that have to be explained.

The data regarding the question, whether a partial adrenal resection including the adenoma is sufficient, is controversial. Some studies reported comparable results after adrenalectomy or partial resection, but others reported higher recurrence rates after parenchymal sparing resection [15, 48–50]. The only prospective randomized study with 212 patients showed no differences regarding the postoperative functional result after partial or total adrenalectomy [51]. If a partial adrenal resection is considered, intraoperative ultrasound should be used to ensure that the adenoma carrying adrenal part will be resected.

Cushing's syndrome

R21: It has to be differentiated preoperatively between ACTH-dependent (Morbus Cushing, paraneoplastic ectopic ACTH-secretion) and ACTH-independent adrenal hypercortisolism by biochemical functional tests and imaging (consensus+++).

R22: In ACTH-independent adrenal hypercortisolism caused by a unilateral adenoma or a resectable adrenocortical carcinoma, adrenalectomy should be performed (consensus+++).

R23: Bilateral adrenalectomy can be performed after treatment of a persistent Morbus Cushing or a non-resectable ectopic ACTH-producing tumor, if medical treatment is exhausted (consensus+++).

R24: Minimally invasive surgery is to be performed in tumors less than 6 cm in size without suspicion of malignancy (consensus+++).

Commentary

The differential diagnosis of ACTH-dependent vs. ACTH-independent hypercortisolism should be made by determination of the basal ACTH (plasma) and basal cortisol concentration in combination with a dexamethasone suppression test or CRF stimulation test [52–54]. In general, every Cushing's syndrome should be treated. An indication for adrenalectomy is always given in case of a unilateral adenoma or resectable adrenocortical carcinoma. In case of a primary hyperplasia of the adrenal cortex, persistent Morbus Cushing after treatment of the pituitary gland or non-resectable ectopic ACTH-producing tumor, bilateral adrenalectomy can be indicated to remove the target organs. The indication for bilateral adrenalectomy should always be weighted very carefully despite its effective treatment of hypercortisolism, since this operation results in a life-long necessity for medical substitution of the adrenal cortex and has a high risk for the development of an ACTH-producing tumor of the pituitary [55–57] (Nelson tumor). In cases of an adrenal tumor < 6 cm in size without suspicion of malignancy as well as in adrenal hyperplasia, minimally invasive adrenalectomy is to be performed.

Adrenal tumors with androgene/estrogene overproduction

R25: Any androgene- or estrogene-producing adrenal tumor should be operated (consensus+++).

In all androgene- or estrogene-producing adrenal tumors adrenal carcinoma must be considered because adenomas are rare (consensus+++).

Depending on the tumor size (up to 6 cm), and in absence of infiltration or lymph node involvement, minimally invasive adrenalectomy can be performed (consensus++).

In suspicion of underlying adrenocortical cancer (ACC), locoregional lymphadenectomy should be performed (consensus++).

Commentary

Adrenal disease with overproduction of androgene or estrogene clinically presents in congenital enzymatic defect of the adrenal steroid biosynthesis, called adrenocortical syndrome (AGS) or in adrenal tumor with increased production of adrenal sex hormones (carcinoma, rarely adenoma). Only adrenal tumors are indication for surgery that is mostly carcinoma; AGS without adrenal tumor is treated medically [58]. All adrenal tumors with sex hormone production represent an indication for surgery irrespective of tumor size due to the risk of malignancy [8, 59–61].

Pheochromocytoma and paraganglioma

R26: In suspicion of pheochromocytoma or paraganglioma by clinical or imaging criteria, the assessment of metanephrines (metanephrine, normetanephrine) in plasma-free serum represents the method of choice (consensus+++).

R27: Patients with 2–3-fold elevation of metanephrines should undergo repeat assessment after horizontal rest and repeat after another 6 months. In case ambiguous results persist, clonidine test can be considered (consensus+++).

R28: Whenever metanephrines exceed 3-fold normal range, imaging diagnostics (CT/MRI) should beinitiated (consensus+++).

R29: Primary choice for imaging is abdominal CT. In pregnancy, children, and patients with contrast media intolerance or previous relevant radiation exposure, MRI should alternatively be used (consensus+++).

In extraadrenal tumors, recurrence, or metastases, MRI is favored over CT due to the higher sensitivity (consensus+++).

In case of dubious findings or in clarification of metastases, additional functional imaging with ^{123}iodine-metaiodobenzyleguanidine (MIBG)-scintigraphy, ^{18}F-fluorodeoxyglucose (FDG) PET/CT, or ^{18}F-fluorodihydroxyphenylalanine (DOPA)-PET/CT should be performed due to the higher specificity (consensus+++).

R30: In proven pheochromocytoma and/or extracervical paraganglioma, surgery should be performed (consensus+++).

Patients with symptomatic pheochromocytoma or paraganglioma should undergo preoperative alpha-blockade. In asymptomatic patients without hypertension (mainly VHL and paranglioma), it may be considered to dispense with preoperative alpha-blockade (consensus+++).

In unilateral pheochromocytoma < 6 cm, minimally invasive adrenalectomy should be performed. For tumors > 6 cm and/or in presence of metastases, open surgery should be performed (consensus++).

In bilateral hereditary pheochromocytoma, adrenal resection with preservation of at least one third of a unilateral adrenal parenchyma should be performed in order to preclude postoperative adrenal insufficiency (consensus+++).

In accordance with tumor localization and surgeon's experience, abdominal paraganglioma may be operated minimally invasively or via an open approach (consensus+++).

In accordance with tumor localization and surgeon's experience, thoracic and mediastinal paraganglioma may be operated minimally invasively by thoracic or open approach (consensus+++).

Commentary

Assessments of metanephrines in plasma-free serum or 24-h urine are the superior tests when pheochromocytoma (PCC) or paranglioma (PGL) is suspected [62, 63], ideally performed in liquid-chromatographic method (LC-ECD or LC-MS/MS) that may even be assessed in saliva probes [64]. Clonidine suppression test may discriminate false from correct positive result in patients with 2–3-fold elevated metanephrines after repeat assessment in horizontal position and resting [65–67].

First imaging choice is CT with a sensitivity of 88–100% revealing typical PCC/PGL features of regressive alterations like necrosis, calcification, and cysts with density > 10 HU without contrast media [68, 69]. CT sensitivity is lower (57%) for extraadrenal tumors, recurrence, and metastases; therefore, MRI is preferable [70] and is alternatively performed whenever CT is unfavorable. Functional confirmation of PCC/PGL with superior specificity may be achieved with ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, ^{18}F-fluorodeoxyglucose (FDG) PET/CT, or ^{18}F-fluorodihydroxyphenylalanine (DOPA)-PET/CT [71, 72]. Unequivocal biochemical evidence with typical adrenal imaging does not require functional imaging. This is, however, recommended in young patients, suspicion of metastases, large or multifocal tumors, extraadrenal manifestation, and syndromatic disease (MEN 2 A/B, VHL, NF1, SDH-mutation) for which MIBG scintigraphy is first choice, if negative ^{18}F-FDG-PET or ^{18}F-DOPA-PET should be performed, also preparing basis for tumor follow-up imaging [73–75].

In proven evidence of pheochromocytoma and/or paraganglioma, indication to surgery is generally given due to the cardiovascular morbidity and mortality of uncontrolled catecholamine secretion as well as for local tumor growth and malignant potential [72]. In metastasized PCC/PGL, surgery aims to prevent local complication, reduce hormone production, and improve successive therapeutic measures [73, 76, 77]. Surgery of a catecholamine producing tumor should only be undertaken after sufficient alpha-blockade. In selective cases without arterial hypertension, this may be dispensed with. In coexistent tachycardia and arrhythmia, additional beta-blockade following sufficient alpha-blockade should be provided [72, 78, 79]. Open surgery should be performed in suspicion of malignant disease or whenever capsular rupture is anticipated. Adrenal preserving resection is considered for bilateral hereditary adrenal PCC, ideally in benign eccentric localized tumors to prevent postoperative adrenal insufficiency at the risk of a higher recurrence rate [72, 80, 81].

Nonfunctioning adrenocortical adenomas

R31: All patients with adrenal tumors should preoperatively undergo clinical, biochemical, and radiological evaluation to confirm or exclude hormonal activity and/or malignancy (consensus+++).

R32: Non-functioning adrenal tumors ≥ 6 cm should be operated because of the increased risk for malignancy. For tumors between 4 and 6 cm in size no clear recommendation can be made, the decision has to be done individually (consensus+++).

R33: The indication for surgery of non-functioning adrenal tumors less than 4 cm in size has to be specifically explained (consensus+++).

R34: Non-functioning adrenal tumors without suspicion of malignancy < 6 cm in size shall be operated via a minimally invasive approach (consensus+++).

Commentary

Non-functioning adrenal adenomas are often detected incidentally by cross-sectional imaging which is primarly not performed to diagnose adrenal disease or for tumor staging [82]. The prevalence of these adrenal incidentalomas > 1 cm ranges between 1.4 and 8.7% depending on age [83–85]. The workup of adrenal incidentaloma has to answer the following questions:

- Is the tumor hormonally active?
- Does the tumor exhibit radiological characteristics that indicate malignancy?
- Does the patient have a personal or familial history of cancer?

According to the European Guideline "incidentaloma," the hormonal activity of each adrenal incidentaloma > 1 cm has to be evaluated by an endocrinological biochemical workup. This has to include a dexamethasone suppression test to exclude an adrenal Cushing's syndrome, determination of free metanephrines in plasma to exclude a pheochromocytoma, and in hypertensive patients, the determination of the aldosterone–renin quotient to exclude a Conn syndrome. If the imaging gives any suspicion for adrenocortical carcinoma, DHEAS, 17-OH-progesteron, and estradiol should be determined in serum [86]. If the presence of a metastasis cannot be excluded by imaging, a fine needle aspiration of the adrenal

tumor can be considered [86, 87]. Before any adrenal puncture, pheochromocytoma has to be biochemically excluded.

Surgery has to be indicated in all non-functioning adrenal tumors ≥ 6 cm, since the risk of malignancy is about 25% [88]. Based on the available data, no definitive recommendation can be given for adrenal tumors between 4 and 6 cm without radiological suspicion of malignancy [86]. An individual approach, either surveillance or minimally invasive adrenalectomy, has to be discussed with the patient. Since there is very low risk of malignancy in non-functioning adrenal tumors < 4 cm (< 2%), there is in general no indication for resection of these tumors. Non-functioning adrenal tumors without suspicion of malignancy should be operated minimally invasively up to a size of 6 cm, since several large retrospective case series have shown that the minimally invasive approach (laparoscopically, retroperitoneoscopically) has advantages with regard to pain, convalescence, hospital stay, and development of incisional hernias [89, 90]. Larger tumors up to 10 cm without suspicion of malignancy may also be operated via a minimally invasive approach, provided the expertise of the surgeon is given [91].

Adrenocortical carcinoma

R35: The initial preoperative biochemical diagnostic workup should be performed in parallel to the imaging and has to include at least a 1-mg dexamethasone-suppression test, determination of plasma or urine metanephrines, sexual hormone, and steroid precursors. In hypertensive and/or hypocalemic patients, the aldosterone/renin-quotient should also be determined (consensus+++).

R36: Preoperatively, an intravenous contrast-enhanced CT or MRI of the abdomen and a CT of the thorax should be performed to determine tumor extension. In suspicion of bone metastasis a bone scintigraphy should be performed. An FDG-PET-CT can be considered (consensus+++).

R37: Surgery has to be indicated, if no distant metastases are present (consensus+++).

R38: ACC should only be operated in centers with more than ten adrenalectomies per year and a high expertise in surgical visceral oncology (consensus+++).

R39: Standard treatment is open en bloc resection of the tumor with its surrounding fatty tissue, using an abdominal or thoraco-abdominal incision. Rupture of the tumor capsule has to be avoided. Thus, parenchymal-sparing resections are contraindicated (consensus+++).

R40: ACC in stage 1 or stage 2 up to 10 cm can be operated via a minimally invasive approach, if the expertise to fulfill all oncological principals is given and if the patient is informed about the potential risks (consensus+++).

R41: In suspicion of infiltration of neighboring organs, en bloc resection has to be performed (consensus+++).

R41: In case of enlarged lymph nodes, a locoregional lymphadenectomy has to be performed (consensus+++).

R44: The resection of primarily unresectable infiltrative or metastasized ACC can be considered, if the tumor shows an objective regression after neoadjuvant chemotherapy, and a radical resection appears possible (consensus+++).

R45: Local recurrences should be operated, if they occur after more than 12 months latency and if they appear resectable (consensus+++).

R46: A cytoreductive resection (R2 resection) can be considered in case of a severe endocrine syndrome caused by hormonal excess that cannot be controlled by medical treatment and survival of more than 6 months can be expected (consensus+++).

Commentary

The working group adrenocortical cancer of the European Network for the Study of Adrenal Tumors (ENSAT) and the European Society of Endocrine Surgeons (ESES) recommended standards for the biochemical workup of suspected ACC [8]. Goal is the structured evaluation of any hormonal dysfunction. The workup includes a dexamethasone suppression test, free cortisol in 24 h urine, basal cortisol level and basal ACTH level in plasma and serum, sexual hormones, and their precursors (e.g., DHEAS) in serum, mineralocorticoids, the aldosterone-renin quotient in case of hypertension and hypokalemia, and an excess of catecholamines (normetanephrine and methoxytyramine in plasma) [92]. For the clarification of the dignity of the adrenal tumor, cross-sectional imaging should be performed. The most important imaging modality is contrast-enhanced CT. Density levels > 10 Hounsfield units in native phase and a washout rate of < 50% after 15 min. indicate a malignant process and need further clarification [93, 94]. Equally effective is modern MRI imaging with dynamic gadolinium enhancement and chemical shift technique [95]. For functional imaging, the ^{18}FDG-PET is currently most valued. It allows whole body staging with regard to metastasis. The preoperative staging to clarify the presence of metastatic disease should include CT of the abdomen and thorax [8, 96]. In proposed stages 1 and 2, adrenalectomy is the treatment of choice. The complete resection of the tumor with the surrounding paraadrenal and perirenal fat tissue should be performed. An incomplete resection, rupture of the tumor capsule or an R2 resection should be avoided in all circumstances, since these are associated with higher recurrence rate and with inferior survival [8, 97, 98]. Several groups suggest that ACC should be only operated in institutions that either perform more than 4 ACC operations per year or more than 15 adrenalectomies for different indications per year [8, 12, 99]. Since there is always the possibility of necessary multivisceral resection, this expertise has to be provided in centers that operate on ACC. In case of a tumor

thrombosis that reaches the inferior vena cava or the right atrium, this might require the use of the heart–lung machine or the replacement of the vena cava. The standard incision should be a median laparotomy or in big tumors a thoracoabdominal incision. In ACC stages 1 and 2 up to 10 cm, a laparoscopic approach can be considered, if there is a high laparoscopic expertise and the oncological criteria will be respected. The data with regard to this topic based on retrospective case series are, however, not conclusive. In one retrospective study with 165 patients, including 64 laparoscopically operated patients, a higher local recurrence rate and an inferior overall survival was shown after laparoscopic procedures [100]. A meta-analysis of 673 patients, however, concluded that no definitive conclusion can be drawn due to the highly heterogeneous retrospective data, so that the gold standard should be the open adrenalectomy [97]. In case of invasion of the ipsilateral kidney or another surrounding organ (mostly liver, pancreas tail or spleen), simultaneous en bloc resection of these organs should be performed to avoid rupture of the tumor capsule. Routine nephrectomy is not recommended, since the influence on overall survival is not proven [101]. Even in cases of infiltration of the renal vein, vena cava or a tumor thrombus which extends into the vena cava or sometimes into the right atrium a R0 resection should be achieved, since the 5-year survival rates are up to 29% [102, 103]. The incidence of lymph node metastasis varies between 10 and 70% [104–107]. In large cohorts from the USA and France, the rate of lymphadenectomy during the primary resection was only 30% [108, 109]. The German ACC registry showed that the resection of more than five lymph nodes reduces the risk of a local recurrence and the overall mortality [97]. Lymph node metastases are most frequently found in the perirenal, paraaortal, and paracaval lymph nodes [109]. As yet, there are no clear recommendations which lymph node stations and how many lymph nodes should be removed. The ENSAT/ESES guidelines recommend a lymph node dissection in the ipsilateral kidney hilus at the origin of the kidney vessels as well as ipsilateral paraaortal and paracaval region [8]. Lymphadenectomy should especially remove lymph nodes that are enlarged on preoperative imaging. A neoadjuvant therapy can be considered in so-called borderline resectable ACC [110, 111]. In one small retrospective study, 13 of 15 ACC could be resected after neoadjuvant treatment and the median disease-free survival was 28 months [111]. A local recurrence occurs in 20–60% of patients [112, 113]. The decision for reoperation should only be made, if an R0 resection appears possible and the anticipated morbidity is low. Patients with a local recurrence within 6 months after primary resection have a poor prognosis, so that the indication for reoperation should be very restrictive. A resection of metastasis should be only performed in patients with a low Ki-67 index and development of their metastasis at least 12 months after the primary resection, since these patients might have a survival benefit compared to medical treatment only [8, 114–117]. It is evident that patients who underwent only R2 resection have a similar poor prognosis like patients who had no surgery [118]. In case of otherwise untreatable hormonal excess, however, a debulking of at least 80% of the tumor burden can be considered to achieve symptom control [119].

Ganglioneuroma, neuroblastoma and myelolipoma

R51: For adrenal neuroblastoma therapy must follow risk adaption (resection only or in combination with chemo-, radiation-, or MIBG-therapy (consensus+++).

R52: In symptomatic ganglioneuroma, resection is indicated (consensus+++).

R53: Symptomatic myelolipoma should be resected (consensus+++).

Commentary

Neuroblastomas are malignant tumors of infancy that most frequently manifest in the adrenal. Prognosis and therapy are linked to MYCN mutation, and patients should be registered in a study for risk-adapted therapy (NB2004) involving resection, chemotherapy, external radiation, and MIBG-therapy or a combination of these [120].

Ganglioneuroma are rare, mostly benign, sometimes hormone producing tumors of the autonomous nerve system, evolving during childhood. Primary therapy is resection in symptomatic tumors [121].

Adrenal myelolipoma are rare functional inactive and mostly asymptomatic benign tumors containing mature adipose and hematopoetic tissue evolving in the fifth to seventh decade. Large tumors, necrosis, or bleeding may cause pain, thus representing indication to resection [122].

Adrenal metastases

R54: Patients with a history of malignant disease should be evaluated for adrenal metasasis when an adrenal lesion does not meet adenoma characteristics on imaging (consensus+++).

R55: Standard evaluation for defining the nature of the adrenal lesion should be abdominal CT or MRI. In suspicion of adrenal metastasis, FDG-PET/CT should be added (consensus+++).

R56: In case imaging remains ambiguous, CT- or ultrasonsography-guided biopsy of the adrenal lesion may be considered after pheochromocytoma is ruled out (consensus+++).

R57: For isolated adrenal metastasis, adrenalectomy can be indicated (consensus+++).

Indication for adrenalectomy for adrenal metastases should be established in interdisciplinary tumor board (consensus+++).

R58: Resection of adrenal metastases should be performed minimally invasively, whenever complete safe resection without spillage can be facilitated. Open surgery should be restricted to rare cases with signs of local infiltration or lesion size > 6 cm (consensus+++).

R59: In inoperable patients, radio-frequency ablation (RFA) as alternative to surgery may be considered (consensus+++).

Commentary

Secondary to benign non-functional adenomas adrenal metastases are the most frequent adrenal tumors [23, 123]. However, even in previous malignancy, 48% of adrenal lesions are benign "incidentalomas" [124]. Origins of adrenal metastases are mainly non-small cell bronchial carcinoma (NSCLC) and breast cancer, but malignant melanoma, hepatic cell carcinoma, and renal cell cancer are also found [23, 125]. In bilateral adrenal lesions, evaluation of adrenal insufficiency is reasonable [97]. Fat content in CT and MRI is critical in differentiation of adrenal adenoma vs. metastasis (low); similarly, high metabolic activity in FDG-PET/CT is found in metastasis rather than in adenoma [126–129]. Oncologic benefit of adrenalectomy in adrenal metastases remains unclear for most cases; therefore, interdisciplinary tumor board counseling is recommended. Some data show adrenalectomy to be a good prognostic marker for all-over survival in certain primary tumors [130–132].

Perioperative management

Primary hypoaldosteronism

R61: Hypokalemia should preoperatively be compensated (consensus+++).

In PHA administration of aldosterone antagonists should be stopped preoperatively for at least 2 weeks in order to compensate hypokalemia (consensus+++).

In patients with unilateral aldosterone producing adenoma (APA), potassium substitution and aldosterone antagonist can be stopped directly with surgery (consensus+++).

In patients with persistent hyperaldosteronism requiring continuation of aldosterone antagonist therapy, slowly increased titration with spironolactone should be first choice (consensus+++).

In very young patients with PHA or in families with several affected individuals, and in case of cerebrovascular infarction at ≤ 40 years, genetic testing (FH-I, FH-III) should be initiated (consensus+++).

Commentary

Preoperative low potassium concentration is frequent in PHA, pronouncedly in APA and is associated with elevated perioperative risk. Compensation can be achieved with potassium substitution and/or administration of aldosterone antagonists [30, 133]. Spironolactone offers good correction of hypertension as well as correcting low potassium; therefore, preoperative treatment, namely in unilateral APA, is efficient [134]. Early postoperative controls of aldosterone and renin level are advised [133]. Postoperative adaption of potassium, antihypertensive medication, and specific diets need to be individually addressed [133, 135–140].

Cortisol-producing adrenal tumors (Cushing's syndrome)

R62: Preoperative treatment to regulate hypertension, compensate electrolytes, and correct diabetes should be initiated (consensus+++).

Susceptibility for infectious disease must be addressed with "single-shot" antibiotic prophylaxis perioperatively, whereas other forms of adrenelactomy do not require antibiotic prophylaxis (consensus++).

Inhibition of steroid synthesis (e.g., ketoconazole) should be avoided due to potential intraoperative side-effects (consensus+++).

Following resection of a cortisol-producing adrenal tumor, consistent postoperative glucocorticoid substitution is obligatory, if necessary adapted to stress (e.g., infection, surgery) and completed with mineralocorticoids. It is compulsory to inform and instruct the patient specifically in these regards. The patient must be supervised by an endocrinologist (consensus+++).

Following bilateral adrenalectomy permanent substitution of glucocorticoids at basal levels, and stress-adapted elevation of dose alongside mineralcorticoid substitution must be provided. The patient must be equipped with an emergency certificate. The patient must be supervised by an endocrinologist and requires specific education (consensus+++).

Commentary

Up to 70% of patients with adrenal tumors undergoing surgery reveal hypertension, 19% diabetes, and patients with adrenal Cushing's disease are predominantly affected. Correction of hypertension, hyperglycemia, hypokalemia, and alkalosis before surgery are recommended for all patients undergoing adrenal surgery [86, 141–143]. Postoperative management of cortisol-producing adrenal tumors, irrespective of unilateral or bilateral surgery, requires glucocorticoid substitution until recovery of the hypothalamic-pituitary axis is evident or permanent following bilateral adrenalectomy [144]. Possible abdication or lower dose and abbreviated duration of glucocorticoid substitution may be managed in accordance with ACTH-(synacthene test (tetracosactid)) stimulation test results [16, 145, 146].

Pheochromocytoma and paraganglioma

R63: Patients with symptomatic pheochromocytoma (PCC) and paraganglioma (PGL) should receive preoperative non-selective or selective α-1-receptor blockade. In asymptomatic patients without hypertension (particularly VHL and PGL), it may be considered to abstain from preoperative blockage (consensus+++).

During surgery for PCC, invasive monitoring with arterial blood pressure assessment, central line, and venous catheter must be performed. Emergency medication to treat hypertensive crisis (e.g., nitroprusside) or hypotension (e.g., arterenole) must be immediately accessible (consensus+++).

Following complete resection of localized benign PCC, perioperative α-blockage should be immediately stopped (consensus+++).

All patients with PCC and PGL should be informed and offered genetic testing in order to clarify heredity. The presenting phenotype may assist orientation in decision algorithm (consensus+++).

Postoperative surveillance and follow-up with laboratory controls should be ascertained or delegated to endocrinology for all patients following surgery for PCC and PGL (consensus+++).

Commentary

Generally, patients undergoing surgery for PPC and PGL require preoperative α-blockage in order to prevent hypertensive crisis perioperatively. Advantages initiated a shift to selective competitive α1-receptor blockage from previously universal use of unselective non-competitive α1- + 2-receptor blockage [2, 72, 147]. In selective cases without hypertension or cardiovascular risk factors, preoperative blockage may be omitted [148–150]. Prognostication of intraoperative circulation and blood pressure remains challenging and requires uninterrupted optimal monitoring to enable immediate intervention and close communication between surgeon and anesthesiologist [151]. Postoperative management after complete resection of PCC and PGL is determined by the nature of disease and heredity and oftentimes requires immediate stop of blocking agents [72]. Increasing knowledge of phenotype–genotype correlation in PCC and PGL assists genetic counseling of patients that should generally be offered [152–156]. Biochemical follow-up investigation should be aligned to the nature of disease and the specific differential catecholamine and metabolite profile [72, 156–161].

Adrenocortical carcinoma

R64: In ACC, patients with advanced disease, residual tumor or with suspicion of tumor recurrence, diagnostics, and therapy should be aligned to published guidelines (e.g., Berruti et al., 2012) and involve proficient oncologists/endocrinologists with disease specific expertise with the entity. Basic thoracic CT and abdominal CT/MRI are recommended pre- and every 12 weeks postoperatively for 2 years following initial surgical therapy (consensus+++).

Individual steroid profile should be assessed preoperatively in all patients with suspicion of ACC and be reinvestigated every 12 weeks during 2 years after initial surgery.

Commentary

Rapid progression of ACC necessitates brief intervals in follow-up including thoracic and abdominal CT or MRI and plasma or urine steroid concentrations that need to be known previous to primary surgery in order to guide surveillance according to the individual "steroid profile." After 2 years of follow-up, intervals may be prolonged to 6–12 months and should be maintained for at least 10 years [8, 94].

Compliance with ethical standards

Conflict of interest Lorenz K: no disclosures
Langer P: no disclosures
Niederle B: no disclosures
Alesina P: no disclosures
Holzer, K: holds Bayer shares
Nies C: no disclosures
Musholt Th: no disclosures
Goretzki P: received consultant's + speaker's honorarium from: Sanofi, Ipsen, Novartis GmbH
Rayes N: no disclosures
Quinkler M: received speaker's honorarium from: Shire plc GmbH, Ipsen GmbH
Waldmann J: no disclosures
Simon D: no disclosures
Trupka A: holds Bayer shares
Ladurner R: no disclosures
Hallfeldt K: no disclosures
Zielke A: no disclosures
Saeger W: received grants from: Ipsen, Novo-Nordisk, Novartis GmbH
Pöppel Th: no disclosures
Kukuk G: no disclosures
Hötker A: no disclosures
Schabram P: no disclosures
Schopf S: holds shares from ISAR-U GmbH
Dotzenrath C: no disclosures
Riss P: no disclosures
Steinmüller Th: no disclosures
Kopp I: no disclosures
Vorländer C: received grants from:Olympus GmbH
Walz M: received speaker's honorarium from: Karl Storz GmbH, Medtronic Co.
Bartsch DK: received speaker's honorarium from: Novartis

Ethical standards This article does not contain any studies with animals performed by any of the authors.

This article does not contain any studies with human participants or animals performed by any of the authors.

Appendix

Guideline working group "surgical treatment of adrenal tumors" of the German Society of Endocrine Surgery (CAEK) of the German Society of General and Visceral Surgery (DGAV) (in alphabetical order)

Dr. P. Alesina, Essen
Prof. D.K. Bartsch, Marburg
Prof. C. Dotzenrath, Wuppertal
Prof. P.E. Goretzki, Berlin
Prof. K. Hallfeldt, München
Prof. K. Holzer, Marburg
PD Dr. R. Ladurner, München
Prof. P. Langer, Hanau
Prof. K. Lorenz, Halle
Prof. T.J. Musholt, Mainz
Prof. B. Niederle, Wien
Prof. Chr. Nies, Osnabrück
Prof. N. Rayes, Leipzig
RA P. Schabram, Freiburg
Prof. D. Simon, Duisburg
PD Dr. S. Schopf, Agatharied
Prof. Th. Steinmüller, Berlin
Prof. A.W. Trupka, Starnberg
Dr. C. Vorländer, Frankfurt
Prof. J. Waldmann, Hamburg
Prof. M. Walz, Essen
Prof. A. Zielke, Stuttgart

Delegates from the participating der medical societies and organizations

AWMF, moderator live consnensus conference: Prof. I. Kopp, Marburg

DGAV: represented by the guideline working group of the CAEK

German Society of Endocrinology: Prof. M. Quinkler, Berlin

German Society of Nuclear Medicine: Prof. Dr. Th.Pöppel, Essen

German Society of Pathology: Prof. Saeger, Hamburg

German Society of Radiology: PD R. Guido Kukuk, Bonn, Dr. Andreas Hötker, Zürich

German Society of Medical Oncology: Prof. Heiko Krude, Berlin

Patientent Support Group Network Pituitary and Adrenal Diseases; registered association, Ms. M. Schubert

Participants of the live consensus conference June 6, 2016 in Frankfurt/M

Prof. I. Kopp, AWMF
Dr. P. Alesina, Essen
Prof. D.K. Bartsch, Marburg
Prof. C. Dotzenrath, Wuppertal
Prof. Dr. K. Hallfeldt, München
Prof. K. Holzer, Frankfurt/M.
Prof. P. Langer, Hanau
Prof. K. Lorenz, Halle
Prof. T.J. Musholt, Mainz
Prof. B. Niederle, Wien
Prof. M. Quinkler, Berlin
Prof. N. Rayes, Leipzig
Prof. W. Saeger, Hamburg
RA P. Schabram, Freiburg
Prof. Th. Steinmüller, Berlin
Dr. C. Vorländer, Frankfurt/M.
Prof. J. Waldmann, Hamburg
Prof. M. Walz, Essen
Prof. A. Zielke, Stuttgart

References

1. awmf.org/leitlinien/detail/ll/088-008.html. Accessed 11 Jan 2018
2. Hartel W, Röher HD, Simon D, Frilling A, Rothmund M, Wagner PK, Klempa I, Goretzki PE, Becker HD, Niederle B, Nies C, Wahl RA, Dralle H (2000) Deutsche Gesellschaft für Chirurgie, Leitlinien zur chirurgischen Therapie von Nebennierenerkrankungen. Mitteilung der Deutschen Gesellschaft für Chirurgie 4:G92
3. Palazzo FF, Sebag F, Sierra M, Ippolito G, Souteyrand P, Henry JF (2006) Long-term outcome following laparoscopic adrenalectomy for large solid adrenal cortex tumors. World J Surg 30:893–898
4. Walz MK, Petersenn S, Koch JA, Mann K, Neumann HP, Schmid KW (2005) Endoscopic treatment of large primary adrenal tumours. Br J Surg 92:719–723
5. Tischler AS (2008) Pheochromocytoma and extra-adrenal paraganglioma: updates. Arch Pathol Lab Med 132:1272–1284
6. Walz MK (2012) Minimally invasive adrenal gland surgery. Transperitoneal or retroperitoneal approach? Chirurg 83:536–545
7. Asari R, Koperek O, Niederle B (2012) Endoscopic adrenalectomy in large adrenal tumors. Surgery 152:41–49
8. Gaujoux S, Mihai R (2017) European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma. Joint working group of ESES and ENSAT. Br J Surg 104:358–376
9. Boland GW, Lee MJ, Gazelle GS, Halpern EF, McNicholas MM, Mueller PR (1998) Characterization of adrenal masses using unenhanced CT: an analysis of the CT literature. Am J Roentgenol 171:201–204
10. Israel GM, Korobkin M, Wang C, Hecht EN, Krinsky GA (2004) Comparison of unenhanced CT and chemical shift MRI in evaluating lipid-rich adrenal adenomas. AJR Am J Roentgenol 183:215–219
11. Brix D, Allolio B, Fenske W, Agha A, Dralle H, Jurowich C, Langer P, Mussack T, Nies C, Riedmiller H, Spahn M, Weismann D, Hahner S, Fassnacht M, German Adrenocortical Carcinoma Registry Group (2010) Laparoscopic versus open adrenalectomy for adrenocortical carcinoma: surgical and oncologic outcome in 152 patients. Eur Urol 58:609–615

12. Lombardi CP, Raffaelli M, De Crea C, Boniardi M, De Toma G, Marzano LA, Miccoli P, Minni F, Morino M, Pelizzo MR, Pietrabissa A, Renda A, Valeri A, Bellantone R (2012) Open versus endoscopic adrenalectomy in the treatment of localized (stage I/II) adrenocortical carcinoma: results of a multiinstitutional Italian survey. Surgery 152:1158–1164
13. Brauckhoff M, Gimm O, Thanh PN, Bär A, Ukkat J, Brauckhoff K, Bönsch T, Dralle H (2003) Critical size of residual adrenal tissue and recovery from impaired early postoperative adrenocortical function after subtotal bilateral adrenalectomy. Surgery 134:1020–1028
14. Alesina PF, Hinrichs J, Meier B, Schmid KW, Neumann HP, Walz MK (2012) Minimally invasive cortical-sparing surgery for bilateral pheochromocytomas. Langenbeck's Arch Surg 397:233–238
15. Walz MK (2009) Adrenalectomy for preservation of adrenocortical function. Indication and results. Chirurg 80:99–104
16. Alesina PF, Hommeltenberg S, Meier B, Petersenn S, Lahner H, Schmid KW, Mann K, Walz MK (2010) Posterior retroperitoneoscopic adrenalectomy for clinical and subclinical Cushing's syndrome. World J Surg 34:1391–1397
17. Telenius-Berg M, Ponder MA, Berg B, Ponder BA, Werner S (1989) Quality of life after bilateral adrenalectomy in MEN 2. Henry Ford Hosp Med J 37:160–163
18. Lairmore TC, Ball DW, Baylin SB, Wells SA Jr (1993) Management of pheochromocytomas in patients with multiple endocrine neoplasia type 2 syndromes. Ann Surg 217:595–601
19. Erlic Z, Rybicki L, Peczkowska M, Golcher H, Kann PH, Brauckhoff M, Mussig K, Muresan M, Schaffler A, Reisch N, Schott M, Fassnacht M, Opocher G, Klose S, Fottner C, Forrer F, Plockinger U, Petersenn S, Zabolotny D, Kollukch O, Yaremchuk S, Januszewicz A, Walz MK, Eng C, Neumann HP, European-American Pheochromocytoma Study Group (2009) Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. Clin Cancer Res 15:6378–6385
20. Lowery AJ, Seeliger B, Alesina PF, Walz MK (2017) Posterior retroperitoneoscopic adrenal surgery for clinical and subclinical Cushing's syndrome in patients with bilateral adrenal disease. Langenbeck's Arch Surg 402:775–785
21. Petersenn S, Beckers A, Ferone D, Van der Lely AJ, Bollerslev J, Boscaro M, Brue T, Bruzzi P, Casanueva FF, Chanson P (2015) Therapy of endocrine disease: outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence. Eur J Endocrinol 172:R227–R239
22. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reincke M (2013) Clinical review: outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab 98:3939–3948
23. Sancho JJ, Triponez F, Montet X, Sitges-Serra A (2012) Surgical management of adrenal metastases. Langenbeck's Arch Surg 97: 179–194
24. Vazquez BJ, Richards ML, Lohse CM, Thompson GB, Farley DR, Grant CS, Huebner M, Moreno J (2012) Adrenalectomy improves outcomes of selected patients with metastatic carcinoma. World J Surg 36:1400–1405
25. Bradley CT, Strong VE (2014) Surgical management of adrenal metastases. J Surg Oncol 109:31–35
26. Welch BT, Callstrom MR, Carpenter PC, Wass CT, Welch TL, Boorjian SA, Nichols DA, Thompson GB, Lohse CM, Erickson D, Leibovich BC, Atwell TD (2014) A single-institution experience in image-guided thermal ablation of adrenal gland metastases. J Vasc Interv Radiol 25:593–598
27. Hiramatsu K, Yamada T, Yukimura Y, Komiya I, Ichikawa K, Ishihara M, Nagata H, Izumiyama T (1981) A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity. Arch Intern Med 141:1589–1593
28. Gordon RD, Stowasser M, Rutherfort JC (2001) Primary aldosteronism: are we diagnosing and operating on too few patients? World J Surg 25:941–947
29. Namba K, Tamanaha T, Nakao K, Kawashima ST, Usui T, Tagami T, Okuno H, Shimatsu A, Suzuki T, Naruse M (2012) Confirmatory testing in primary aldosteronism. J Clin Endocrinol Metab 97:1688–1694
30. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM (2008) Case detection, diagnosis and treatment of patients with primary aldosteronism: an Endocrine Society Clinical practise Guideline. J Clin Endocrinol Metab 93:3266–3328
31. Waldmann J, Bartsch DK, Kann PH, Fendrich V, Rothmund M, Langer P (2007) Adrenal involvement in multiple endocrine neoplasia type 1: results of 7 years prospective screening. Langenbeck's Arch Surg 387:437–443
32. Agha A, Hornung M, Iesalnieks I, Schreyer A, Jung EM, Haneya A, Schlitt HJ (2014) Predictors of malignancy in primary aldosteronism. Langenbeck's Arch Surg 399:93–98
33. Rossi GP, Barisa M, Allolio B, Auchus RJ, Amar L, Cohen D, Degenhart C, Deinum J, Fischer E, Gordon R, Kickuth R, Kline G, Lacroix A, Magill S, Miotto D, Naruse M, Nishikawa T, Omura M, Pimenta E, Plouin PF, Quinkler M, Reincke M, Rossi E, Rump LC, Satoh F, Schultze Kool L, Seccia TM, Stowasser M, Tanabe A, Trerotola S, Vonend O, Widimsky J Jr, Wu KD, Wu VC, Pessina AC (2012) The adrenal vein sampling international study AVIS for identifying the major subtypes of primary aldosteronism. J Clin Endocrinol Metab 97:1606–1614
34. Young WF, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA (2004) Role for adrenal venous sampling in primary aldosteronism. Surgery 136:1227–1235
35. Lim V, Guo Q, Grant CS, Thompson GB, Richards ML, Farley DR, Young WF Jr (2014) Accuracy of adrenal imaging an adrenal venous sampling in predicting surgical cure of primary aldosteronism. J Clin Endocrinol Metab 99:2712–2719
36. Tan YY, Ogilvie JB, Triponez F, Caron NR, Kebebew EK, Clark OH, Duh QY (2006) Selective use of adrenal venous sampling in the lateralization of aldosterone-producing adenomas. World J Surg 30:879–887
37. Oh EM, Lee KE, Yoon K, Kim SY, Kim HC, Youn YK (2012) Value of adrenal venous sampling for lesion localization in primary aldosteronism. World J Surg 36:2522–2527
38. Pirvu A, Naem N, Baguet JP, Thony F, Chabre O, Chaffanjon P (2014) Is adrenal venous sampling mandatory before surgical decision in case of primary hyperaldosteronism? World J Surg 38: 1749–1754
39. Volpe C, Enberg U, Sjögren A, Wahrenberg H, Jacobsson H, Törring O, Hamberger B, Thorén M (2008) The role of adrenal scintigraphy in the preoperative management of primary aldosteronism. Scand J Surg 97:248–253
40. Carter Y, Roy M, Sippel RS, Chen H (2012) Persistent hypertension after adrenalectomy for an aldosteron-producing adenoma: weight as a critical prognostic factor for aldosterone's lasting effect on the cardiac and vascular systems. J Surg Res 177:241–247
41. Van der Linden P, Streichen O, Zinzindohoue F, Plouin PF (2012) Blood pressure and medication changes following adrenalectomy for unilateral aldosteronism: a follow-up study. J Hypertens 30: 761–769
42. Wang W, Hu W, Zhang X, Wang B, Bin C, Huang H (2012) Predictors of successful outcome after adrenalectomy for primary aldosteronism. Int Surg 97:104–111
43. Strauch B, Petrak O, Zelinka T, Wichterle D, Holaj R, Kasalicky M, Safarik L, Rosa J, Widimsky J Jr (2008) Adrenalectoy improves arterial stiffness in primary aldosteronism. Am J Hypertens 21:1086–1092

44. Lin YH, Wu XM, Lee HH, Lee JK, Liu YC, Chang HW, Lin CY, Wu VC, Chueh SC, Lin LC, Lo MT, Ho YL, Wu KD, TAIPAI Study Group (2012) Adrenalectomy reverses myocardial fibrosis in patients with primary aldosteronism. J Hypertens 30:1606–1613
45. Tsuchiya K, Yoshimoto T, Hirata Y (2009) Endothelial dysfunction is related to aldosterone excess and raised blood pressure. Endocr J 56:553–559
46. Magill SB, Raff H, Shaker JL, Brickner RC, Knechtges TE, Kehoe ME, Findling JW (2001) Comparison of adrenal vein sampling and computed tomography in the differentiation of primary aldosteronism. J Clin Endocrinol Metab 86:1066–1071
47. Steichen O, Zinzindohoué F, Plouin PF, Amar L (2012) Outcomes of adrenalectomy in patients with unilateral primary aldosteronism: a review. Horm Metab Res 44:221–227
48. Walz MK, Gwosdz R, Levin SL, Alesina PF, Suttorp AC, Metz KA, Wenger FA, Petersenn S, Mann K, Schmid KW (2008) Retroperitoneoscopic adrenalectomy in Conn's syndrome caused by adrenal adenomas or nodular hyperplasia. World J Surg 32:847–853
49. Ishidoya S, Ito A, Sakai K (2005) Laparoscopic partial versus total adrenalectomy for aldosterone producing adenoma. J Urol 174:40–43
50. Chen SF, Chueh SC, Wang SM, Wu VC, Pu YS, Wu KD, Huang KH (2014) Clinical outcomes in patients undergoing laparoscopic adrenalectomy for unilateral aldosterone producing adenoma: partial versus total adrenalectomy. J Endourol 28:1103–1106
51. Fu B, Zhang X, Wang GX, Lang B, Ma X, Li HZ, Wang BJ, Shi TP, Ai X, Zhou HX, Zheng T (2011) Long-term results of a prospective, randomized trial comparing retroperitoneoscopic partial versus total adrenalectomy for aldosterone producing adenoma. J Urol 185:1578–1582
52. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Endocrine Society (2015) Treatment of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 100:2807–2831
53. Arnaldi G, Trementino L (2016) Update on hypercortisolism therapy. Front Horm Res 46:87–105
54. Buliman A, Tataranu LG, Paun DL, Mirica A, Dumitrache C (2016) Cushing's disease: a multidisciplinary overview of the clinical features, diagnosis, and treatment. J Med Life 9:12–18
55. Young WF Jr, du Plessis H, Thompson GB, Grant CS, Farley DR, Richards ML, Erickson D, Vella A, Stanson AW, Carney JA, Abboud CF, Carpenter PC (2008) The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses. World J Surg 32:856–862
56. Reincke M, Ritzel K, Oßwald A, Berr C, Stalla G, Hallfeldt K, Reisch N, Schopohl J, Beuschlein F (2015) A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing's syndrome. Eur J Endocrinol 173:23–32
57. Seki T, Yasuda A, Kitajima N, Oki M, Takagi A, Nakamura N, Hanai K, Terachi T, Fukagawa M (2015) Adrenal venous sampling is useful for a definitive diagnosis in Cushing's syndrome with bilateral adrenal tumors. Tokai J Exp Clin 40:149–156
58. Lack EE (2007) Tumors of the adrenal glands and the extraadrenal paraganglia. AFIP Atlas of tumor pathology. American Registry of Pathology, Armed Forces Institute of Pathology, Washington, pp 1–500
59. Gaujoux S, Brennan MF (2012) Recommendation for standardized surgical management of primary adrenocortical carcinoma. Surgery 152:123–132
60. Else T, Kim AC, Sabolch A, Raymond VM, Kandathil A, Caoili EM, Jolly S, Miller BS, Giordano TJ, Hammer GD (2014) Adrenocortical carcinoma. Endocr Rev 35:282–326
61. Stigliano A, Chiodini I, Giordano R, Faggiano A, Canu L, Della Casa S, Loli P, Luconi M, Mantero F, Terzolo M (2016) Management of adrenocortical carcinoma: a consensus statement of the Italian Society of Endocrinology (SIE). J Endocrinol Invest 39:103–121
62. Eisenhofer G, Keiser H, Friberg P, Mezey E, Huynh TT, Hiremagalur B, Ellingson T, Duddempudi S, Eijsbouts A, Lenders JW (1998) Plasma metanephrines are markers of pheochromocytoma produced by catechol-O methyltransferase within tumors. J Clin Endocrinol Metab 83:2175–2185
63. Sawka AM, Jaeschke R, Singh RJ, Young WF (2003) A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 88:553–558
64. Osinga TE, van der Horst-Schrivers AN, van Faassen M, Kerstens MN, Dullart RP, Pacak K, Links TP, Kema IP (2016) Mass spectrometic quantification of salivary metanephrines-a study in healthy subjects. Clin Biochem 49:983–938
65. Eisenhofer G, Goldstein DS, Walther MM, Friberg P, Lenders JW, Keiser HR, Pacak K (2003) Biochemical diagnosis of pheochromocytoma:how to distinguish true- from false positive test results. J Clin Endocrinol Metab 88:2656–2666
66. Därr R, Lenders JW, Stange K, Kindel B, Hofbauer LC, Bornstein SR, Eisenhofer G (2013) Diagnosis of pheochromocytoma and paraganglioma: the clonidine suppression test in patients with borderline elevations of plasma free normetanephrine. Dtsch Med Wochenschr 138:76–81
67. Neary NM, King KS, Pacak K (2011) Drugs and pheochromocytoma—don't be fooled by every elevated metanephrine. N Engl J Med 364:2268–2270
68. Motta-Ramirez GA, Remer EM, Herts BR, Gill IS, Hamrahian AH (2005) Comparison of CT findings in symptomatic and incidentally discovered pheochromocytomas. Am J Roentgenol 185:684–688
69. Blake MA, Krishnamoorthy SK, Boland GW, Sweeney AT, Pitman MB, Harisinghani M, Mueller PR, Hahn PF (2003) Low-density pheochromocytoma on CT: a mimicker of adrenal adenoma. Am J Roentgenol 181:1663–1668
70. Sahdev A, Sohaib A, Monson JP, Grossman AB, Chew SL, Reznek RH (2005) CT and MR imaging of unusual locations of extra-adrenal paragangliomas (pheochromocytomas). Eur Radiol 15:85–92
71. Van Berkel A, Pacak K, Lenders JWM (2014) Should every patient diagnosed with a pheochromocytoma have a 123I-MIBG scintigraphy? Clin Endocrinol 81:329–333
72. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF (2014) Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 99:1915–1942
73. Shulkin BL, Thompson NW, Shapiro B, Francis IR, Sisson JC (1999) Pheochromocytomas: imaging with 2-[fluorine-18]fluoro-2-deoxy-D-glucose PET. Radiology 212:35–41
74. Mann GN, Link JM, Pham P, Pickett CA, Byrd DR, Kinahan PE, Krohn KA, Mankoff DA (2006) [11C]metahydroxyephedrine and [18F]fluorodeoxyglucose positron emission tomography improve clinical decision making in suspected pheochromocytoma. Ann Surg Oncol 13:187–197
75. Timmers HJ, Eisenhofer G, Carrasquillo JA, Chen CC, Whatley M, Ling A, Adams KT, Pacak K (2009) Use of 6-[18F]-fluorodopamine positron emission tomography (PET) as first-line investigation for the diagnosis and localization of non-metastatic and metastatic phaeochromocytoma (PHEO). Clin Endocrinol 71:11–17
76. Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, Gimenez-Roqueplo AP, Grossman AB, Kimura N, Mannelli M, McNicol AM, Tischler AS (2007) Pheochromocytoma: recommendations

for clinical practice from the First International Symposium. Nat Clin Pract Endocrinol Metab 3:92–102
77. Ellis RJ, Patel D, Prodanov T, Sadowski S, Nilubol N, Adams K, Steinberg SM, Pacak K, Kebebew E (2013) Response after surgical resection of metastatic pheochromocytoma and paraganglioma: can postoperative biochemical remission be predicted? J Am Coll Surg 217:489–496
78. Stefanidis D, Goldfarb M, Kercher KW, Hope WW, Richardson W, Fanelli RD (2013) SAGES guidelines for minimally invasive treatment of adrenal pathology. Surg Endosc 27:3960–3980
79. Walz MK, Peitgen K, Neumann HP, Janssen OE, Philipp T, Mann K (2002) Endoscopic treatment of solitary, bilateral, multiple, and recurrent pheochromocytomas and paragangliomas. World J Surg 26:1005–1012
80. Brunt LM, Lairmore TC, Doherty GM, Quasebarth MA, DeBenedetti M, Moley JF (2002) Adrenalectomy for familial pheochromocytoma in the laparoscopic era. Ann Surg 235:713–720
81. Yip L, Lee JE, Shapiro SE, Waguespack SG, Sherman SI, Hoff AO, Gagel RF, Arens JF, Evans DB (2004) Surgical management of hereditary pheochromocytoma. J Am Coll Surg 198:525–534
82. Young WF (2007) The incidentally discovered adrenal mass. N Engl J Med 356:601–610
83. Reincke M, Slawick M Adrenal incidentalomas. In: De Groot LJ, Beck-Peccoz P, Chrousos G, Dungan K, Grossman A, Hershman JM, Koch C, McLachlan R, New M, Rebar R, Singer F, Vinik A, Weickert MO (eds) Endotext [Internet]. MDText.com, Inc., South Dartmouth, pp 2000–2010
84. Terzolo M, Stigliano A, Chiodini I, Loli P, Furlani L, Arnaldi G, Reimondo G, Pia A, Toscano V, Zini M, Borretta G, Papini E, Garofalo P, Allolio B, Dupas B, Mantero F, Tabarin A (2011) Italian Association of Clinical Endocrinologists (AME) position statement on adrenal incidentaloma. Eur J Endocrinol 164:851–870
85. Petersenn S, Richter PA, Broemel T, Ritter CO, Deutschbein T, Beil FU, Allolio B, Fassnacht M, German ACC Study Group (2015) Computed tomography criteria for discrimination of adrenal adenomas and adrenocortical carcinomas: analysis of the German ACC registry. Eur J Endocrinol 172:415–422
86. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM (2016) Management of adrenal incidentalomas: European Society of Endocrinology clinical practice guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 175:G1–G34
87. Kapoor A, Morrios T, Rebello R (2011) Guidelines for the managemnet of the incidentally discovered adrenal mass. Can Urol Assoc J 5:241–247
88. Grumbach MM, Biller BM, Braunstein GD, Campbell KK, Carney JA, Godley PA, Harris EL, Lee JK, Oertel YC, Posner MC, Schlechte JA, Wieand HS (2003) Management of the clinically inapparent adrenal mass ("incidentaloma"). Ann Intern Med 138:424–429
89. Fernández-Cruz L, Sáenz A, Benarroch G, Sabater L, Taurá P (1996) Does hormonal function of the tumor influence the outcome of laparoscopic adrenalectomy? Surg Endosc 10:1088–1091
90. Shen WT, Lim RC, Siperstein AE, Clark OH, Schecter WP, Hunt TK, Horn JK, Duh QY (1999) Laparoscopic vs open adrenalectomy for the treatment of primary hyperaldosteronism. Arch Surg: 134628–134631
91. Natkaniec M, Pędziwiatr M, Wierdak M (2016) Laparoscopic transperitoneal lateral adrenalectomy for large adrenal tumors. Urol Int 97:165–172
92. Arlt W, Biehl M, Taylor AE, Hahner S, Libé R, Hughes BA, Schneider P, Smith DJ, Stiekema H, Krone N, Porfiri E, Opocher G, Bertherat J, Mantero F, Allolio B, Terzolo M, Nightingale P, Shackleton CH, Bertagna X, Fassnacht M, Stewart PM (2011) Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. J Clin Endocrinol Metab 96:3775–3784
93. Zhang HM, Perrier ND, Grubbs EG, Sircar K, Ye ZX, Lee JE, Ng CS (2012) CT features and quantification of the characteristics of adrenocortical carcinomas on unenhanced and contrast-enhanced studies. Clin Radiol 67:38–46
94. Young WF Jr (2011) Conventional imaging in adrenocortical carcinoma: update and perspectives. Horm Cancer 2:341–347
95. Bharwani N, Rockall AG, Sahdev A, Gueorguiev M, Drake W, Grossman AB, Reznek RH (2011) Adrenocortical carcinoma: the range of appearances on CT and MRI. Am J Roentgenol 196:706–714
96. Berutti A, Baudin E, Gelderblum H, Haak HR, Porpiglia F, Fassnacht M, Pentheroudakis G (2012) Adrenal Cancer: ESMO Clincal Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 23(Suppl 7):131–138
97. Reibetanz J, Jurowich C, Erdogan I, Nies C, Rayes N, Dralle H, Behrend M, Allolio B, Fassnacht M, German ACC Study Group (2012) Impact of lymphadenectomy on the oncologic outcome of patients with adrenocortical carcinoma. Ann Surg 255:363–369
98. Freire DS, Siqueira SA, Zerbini MC, Wajchenberg BL, Corrêa-Giannella ML, Lucon AM, Pereira MA (2013) Development and internal validation of an adrenal cortical carcinoma prognostic score for predicting the risk of metastasis and local recurrence. Clin Endocrinol 79:468–745
99. Gratian L, Pura J, Dinan M, Reed S, Scheri R, Roman S, Sosa JA (2014) Treatment patterns and outcomes for patients with adrenocortical carcinoma associated with hospital case volume in the United States. Ann Surg Oncol 213:509–514
100. Miller BS, Gauger PG, Hammer GD, Doherty GM (2012) Resection of adrenocortical carcinoma is less complete and local recurrence occurs sooner and more often after laparoscopic adrenalectomy than after open adrenalectomy. Surgery 152:1150–1157
101. Porpiglia F, Fiori C, Daffara FC, Zaggia B, Ardito A, Scarpa RM, Papotti M, Berruti A, Scagliotti GV, Terzolo M (2016) Does nephrectomy during radical adrenalectomy for stage II adrenocortical cancer affect patient outcome? J Endocrinol Investig 39:465–471
102. Turbendian HK, Strong VE, Hsu M, Ghossein RA, Fahey TJ 3rd (2010) Adrenocortical carcinoma: the influence of large vessel extension. Surgery 148:1057–1064
103. Mihai R, Iacobone M, Makay O, Moreno P, Frilling A, Kraimps JL, Soriano A, Villar del Moral J, Barczynski M, Durán MC, Sadler GP, Niederle B, Dralle H, Harrison B, Carnaille B (2012) Outcome of operation in patients with adrenocortical cancer invading the inferior vena cava-a European Society of Endocrine Surgeons (ESES) survey. Langenbeck's Arch Surg 397:225–231
104. Fassnacht M, Kroiss M, Allolio B (2013) Update in adrenocortical carcinoma. J Clin Endocrinol Metab 98:4551–4564
105. Saade N, Sadler C, Goldfarb M (2015) Impact of regional lymph node dissection on disease specific survival in adrenal cortical carcinoma. Horm Metab Res 47:820–825
106. Mihai R (2015) Diagnosis, treatment and outcome of adrenocortical cancer. Br J Surg 102:291–306
107. Nilubol N, Patel D, Kebebew E (2016) Does lymphadenectomy improve survival in patients with adrenocortical carcinoma? A population-based study. World J Surg 40:697–705
108. Bilimoria KY, Shen WT, Elaraj D, Bentrem DJ, Winchester DJ, Kebebew E, Sturgeon C (2008) Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. Cancer 113:3130–3136
109. Icard P, Goudet P, Charpenay C, Andreassian B, Carnaille B, Chapuis Y, Cougard P, Henry JF, Proye C (2001) Adrenocortical

carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg 25:891–897
110. Polat B, Fassnacht M, Pfreundner L, Guckenberger M, Bratengeier K, Johanssen S, Kenn W, Hahner S, Allolio B, Flentje M (2009) Radiotherapy in adrenocortical carcinoma. Cancer 115:2816–2823
111. Bednarski BK, Habra MA, Phan A, Milton DR, Wood C, Vauthey N, Evans DB, Katz MH, Ng CS, Perrier ND, Lee JE, Grubbs EG (2014) Borderline resectable adrenal cortical carcinoma: a potential role for preoperative chemotherapy. World J Surg 38:1318–1327
112. Bellantone R, Ferrante A, Boscherini M, Lombardi CP, Crucitti P, Crucitti F, Favia G, Borrelli D, Boffi L, Capussotti L, Carbone G, Casaccia M, Cavallaro A, Del Gaudio A, Dettori G, Di Giovanni V, Mazziotti A, Marrano D, Masenti E, Miccoli P, Mosca F, Mussa A, Petronio R, Piat G, Ruberti U, Serio G, Marzano L (1997) Role of reoperation in recurrence of adrenal cortical carcinoma: results from 188 cases collected in the Italian National Registry for Adrenal Cortical Carcinoma. Surgery 122:1212–1218
113. Fassnacht M, Hahner S, Polat B, Koschker AC, Kenn W, Flentje M, Allolio B (2006) Efficacy of adjuvant radiotherapy of the tumor bed on local recurrence of adrenocortical carcinoma. J Clin Endocrinol Metab 91:4501–4504
114. Kemp CD, Ripley RT, Mathur A, Steinberg SM, Nguyen DM, Fojo T, Schrump DS (2011) Pulmonary resection for metastatic adrenocortical carcinoma: the National Cancer Institute experience. Ann Thorac Surg 92:1195–1200
115. Ripley RT, Kemp CD, Davis JL, Langan RC, Royal RE, Libutti SK, Steinberg SM, Wood BJ, Kammula US, Fojo T, Avital I (2011) Liver resection and ablation for metastatic adrenocortical carcinoma. Ann Surg Oncol 18:1972–1979
116. Kerkhofs TM, Verhoeven RH, Bonjer HJ, van Dijkum EJ, Vriens MR, De Vries J, Van Eijck CH, Bonsing BA, Van de Poll-Franse LV, Haak HR, Dutch Adrenal Network (2013) Surgery for adrenocortical carcinoma in The Netherlands: analysis of the national cancer registry data. Eur J Endocrinol 169:83–89
117. Dy BM, Wise KB, Richards ML, Young WF, Grant CS, Bible KC, Rosedahl J, Harmsen WS, Farley DR, Thompson GB (2013) Operative intervention for recurrent adrenocortical cancer. Surgery 154:1292–1299
118. Erdogan I, Deutschbein T, Jurowich C, Kroiss M, Ronchi C, Quinkler M, Waldmann J, Willenberg HS, Beuschlein F, Fottner C, Klose S, Heidemeier A, Brix D, Fenske W, Hahner S, Reibetanz J, Allolio B, Fassnacht M, German Adrenocortical Carcinoma Study Group (2013) The role of surgery in the management of recurrent adrenocortical carcinoma. J Clin Endocrinol Metab 98:181–191
119. Schteingart DE, Doherty GM, Gauger PG, Giordano TJ, Hammer GD, Korobkin M, Worden FP (2005) Management of patients with adrenal cancer: recommendations of an international consensus conference. Endocr Relat Cancer 12:667–680
120. Hero B, Berthold F (2011) Neuroblastom. Leitlinie der Gesellschaft für Pädiatrische Onkologie und Hämatologie. AWMF-Register Nr. 025/008 online
121. Shawa H, Elsayes KM, Javadi S, Morani A, Williams MD, Lee JE, Waguespack SG, Busaidy NL, Vassilopoulou-Sellin R, Jimenez C, Habra MA (2014) Adrenal ganglioneuroma: features and outcomes of 27 cases at a referral cancer centre. Clin Endocrinol 80:342–347
122. Patel VG, Babalola OA, Fortson JK, Weaver WL (2006) Adrenal myelolipoma: a report of a case and review of the literature. Am Surg 72:649–654
123. Uberoi J, Munver R (2009) Surgical management of metastases to the adrenal gland: open, laparoscopic, and ablative approaches. Curr Urol Rep 10:67–72
124. Lenert JT, Barnett CC Jr, Kudelka AP, Sellin RV, Gagel RF, Prieto VG, Skibber JM, Ross MI, Pisters PW, Curley SA, Evans DB, Lee JE (2001) Evaluation and surgical resection of adrenal masses in patients with a history of extra-adrenal malignancy. Surgery 130:1060–1067
125. Lumb G, Mackenzie DH (1959) The incidence of metastases in adrenal glands and ovaries removed for carcinoma of the breast. Cancer 12:521–526
126. Korobkin M, Giordano TJ, Brodeur FJ, Francis IR, Siegelman ES, Quint LE, Dunnick NR, Heiken JP, Wang HH (1996) Adrenal adenomas: relationship between histologic lipid and CT and MR findings. Radiology 200:743–747
127. Caoili EM, Korobkin M, Francis IR, Cohan RH, Platt JF, Dunnick NR, Raghupathi KI (2002) Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 222:629–633
128. Haider MA, Ghai S, Jhaveri K, Lockwood G (2004) Chemical shift MR imaging of hyperattenuating (>10 HU) adrenal masses: does it still have a role? Radiology 231:711–716
129. Song JH, Chaudhry FS, Mayo-Smith WW (2008) The incidental adrenal mass on CT: prevalence of adrenal disease in 1,049 consecutive adrenal masses in patients with no known malignancy. Am J Roentgenol 190:1163–1168
130. Pfannschmidt J, Schlolaut B, Muley T, Hoffmann H, Dienemann H (2005) Adrenalectomy for solitary adrenal metastases from non-small cell lung cancer. Lung Cancer 49:203–207
131. Mercier O, Fadel E, de Perrot M, Mussot S, Stella F, Chapelier A, Dartevelle P (2005) Surgical treatment of solitary adrenal metastasis from non-small cell lung cancer. J Thorac Cardiovasc Surg 130:136–140
132. Muth A, Persson F, Jansson S, Johanson V, Ahlman H, Wangberg B (2010) Prognostic factors for survival after surgery for adrenal metastasis. Eur J Surg Oncol 36:699–704
133. Young WF Jr (2003) Primary aldosteronism—changing concepts in diagnosis and treatment. Endocrinology 144:2208–2213
134. Funder JW, Carey RM, Matero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF (2016) Guidelines on primary aldosteronism. J Clin Endocrinol Metab 101:1889–1916
135. Sawka AM, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, van Heerden JA (2001) Primary aldosteronism: factors associated with normalization of blood pressure after surgery. Ann Intern Med 135:258–226
136. Harris DA, Au-Yong I, Basnyat PS, Sadler GP, Wheeler MH (2003) Review of surgical management of aldosterone secreting tumours of the adrenal cortex. Eur J Surg Oncol 29:467–474
137. Lim PO, Young WF, MacDonald TM (2001) A review of the medical treatment of primary aldosteronism. J Hypertens 19:353–361
138. Montori VM, Young WF (2002) Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism: a systematic review of the literature. Endocrinol Metab Clin N Am 31:619–632
139. Parthasarathy HK, Ménard J, White WB, Young WF, Williams GH, Williams B, Ruilope LM, McInnes GT, Connell JM, MacDonald TM (2011) A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens 29:980–990
140. Karagiannis A, Tziomalos K, Papageorgiou A, Kakafika AI, Pagourelias ED, Anagnostis P, Athyros VG, Mikhailidis DP (2008) Spironolactone versus eplerenone for the treatment of idiopathic hyperaldosteronism. Expert Opin Pharmacother 9:509–515
141. Sood A, Majumder K, Kachroo N, Sammon JD, Abdollah F, Schmid M, Hsu L, Jeong W, Meyer CP, Hanske J, Kalu R, Menon M, Trinh QD (2016) Adverse event rates, timing of

complications, and the impact of specialty on outcomes following adrenal surgery: an analysis of 30-day outcome data from the American college of surgeons national surgical quality improvement program (ACS-NSQIP). Urology 90:62–68
142. Niemann LK (2015) Cushing's syndrome: update on signs, symptoms and biochemical screening. Eur J Endocrinol 173:M33–M38
143. Gumbs AA, Gagner M (2006) Laparoscopic adrenalectomy. Best Pract Res Clin Endocrinol Metab 20:483–499
144. Flohr F, Seufert J (2007) Hypophysen- und Nebennierenoperationen. Internist 48:578–585
145. Hahner S, Allolio B (2005) Management of adrenal insufficiency in different clinical settings. Expert Opin Pharmacother 6:2407–2417
146. Ortiz DI, Findling JW, Carroll TB, Javorsky BR, Carr AA, Evans DB, Yen TW, Wang TS (2016) Cosyntropin stimulation testing on postoperative day 1 allows for selective glucocorticoid replacement therapy after adrenalectomy for hypercortisolism: results of a novel, multidisciplinary institutional protocol. Surgery 159:259–266
147. der Zee V, de Boer A (2014) Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. Neth J Med 72:190–201
148. Shao Y, Chen R, Shen ZJ, Teng Y, Huang P, Rui WB, Xie X, Zhou WL (2011) Preoperative alpha blockade for normotensive pheochromocytoma: is it necessary. J Hypertens 29:2429–2432
149. Groeben H, Nottebaum BJ, Alesina PF, Traut A, Neumann HP, Walz MK (2017) Perioperative alpha-receptor blockade in pheochromocytoma surgery: an observational case series. Br J Anaesth 118:182–189
150. Lafont M, Fagour C, Haissaguerre M, Darancette G, Wagner T, Corcuff JB, Tabarin A (2015) Perioperative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas. J Clin Endocrinol Metab 100:417–421
151. Naranjo J, Dodd S, Martin YN (2017) Perioperative management of pheochromocytoma. J Cardiothoracic Vasc Anaest 31:1427–1439. https://doi.org/10.1053/j.jvca2017.02.023
152. Ong KR, Woodward ER, Killick P, Lim C, Macdonald F, Maher ER (2007) Genotype-phenotype correlations in von Hippel-Lindau disease. Hum Mutat 28:143–149
153. Gimenez-Roqueplo AP, Caumont-Prim A, Houzard C, Hignette C, Hernigou A, Halimi P, Niccoli P, Leboulleux S, Amar L, Borson-Chazot F, Cardot-Bauters C, Delemer B, Chabolle F, Coupier I, Libé R, Peitzsch M, Peyrard S, Tenenbaum F, Plouin PF, Chatellier G, Rohmer V (2013) Imaging work-up for screening of paraganglioma and pheochromocytoma in SDHx mutation carriers: a multicenter prospective study from the PGL.EVA Investigators. J Clin Endocrinol Metab 98:162–167
154. Chrisoulidou A, Kaltsas G, Ilias I, Grossman AB (2007) The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr Relat Cancer 14(569):585
155. Amar L, Fassnacht M, Gimenez-Roqueplo AP, Januszewicz A, Prejbisz A, Timmers H, Plouin PF (2012) Long-term postoperative follow-up in patients with apparently benign pheochromocytoma and paraganglioma. Horm Metab Res 44:385–389
156. Favier J, Amar L, Gimenez-Roqueplo AP (2015) Pheochromocytoma and paraganglioma: from genetic to clinics. Nat Rev Endocrinol 11:101–111
157. Eisenhofer G, Lenders JW, Siegert G, Bornstein SR, Friberg P, Milosevic D, Mannelli M, Linehan WM, Adams K, Timmers HJ, Pacak K (2012) Plasma methoxytyramine: a novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and SDHB mutation status. Eur J Cancer 48:1739–1749
158. Eisenhofer G, Peitzsch M (2014) Laboratory evaluation of pheochromocytoma and paraganglioma. Clin Chem 60:1486–1499
159. Neumann HP, Pawlu C, Peczkowska M, Bausch B, McWhinney SR, Muresan M, Buchta M, Franke G, Klisch J, Bley TA, Hoegerle S, Boedeker CC, Opocher G, Schipper J, Januszewicz A, Eng C (2004) Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. J Am Ass Med 292:943–951
160. Rufini V, Treglia G, Castaldi P, Perotti G, Giordano A (2013) Comparison of metaiodobenzyl-guanidine scintigraphy with positron emission tomography in the diagnostic work-up of pheochromocytoma and paraganglioma: a systematic review. Q J Nucl Med Mol Imaging 57:122–133
161. Cascón A, Comino-Méndez I, Currás-Freixes M, de Cubas AA, Contreras L, Richter S, Peitzsch M, Mancikova V, Inglada-Pérez L, Pérez-Barrios A, Calatayud M, Azriel S, Villar-Vicente R, Aller J, Setién F, Moran S, Garcia JF, Río-Machín A, Letón R, Gómez-Graña Á, Apellániz-Ruiz M, Roncador G, Esteller M, Rodríguez-Antona C, Satrústegui J, Eisenhofer G, Urioste M, Robledo M (2015) Whole-exome sequencing identifies MDH2 as a new familial paraganglioma gene. J Natl Cancer Inst 107:5

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.