Human Pathology (2021) **110**, 50–61

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Data set for reporting of carcinoma of the adrenal cortex: explanations and recommendations of the guidelines from the International Collaboration on Cancer Reporting☆

Thomas J. Giordano MD, PhD [a,*], Daniel Berney MA, MB B Chir, FRCPath [b], Ronald R. de Krijger MD, PhD [c], Lori Erickson MD [d], Martin Fassnacht MD [e], Ozgur Mete MD, FRCPC [f], Thomas Papathomas MD, PhD, FRCPath [g], Mauro Papotti MD [h], Hironobu Sasano MD, PhD [i], Lester D.R. Thompson MD [j], Marco Volante MD, PhD [k], Anthony J. Gill MBBS, MD, FRCPA [l,m,n]

[a] *Department of Pathology and Clinical Laboratories, University of Michigan, MI, 48109-5602, USA*
[b] *Department of Cellular Pathology, The Royal London Hospital, Barts Health NHS Trust, London, E1 1BB, UK*
[c] *Department of Pathology, University Medical Centre and Princess Maxima Centre for Pediatric Oncology, 3584 CS, Utrecht, the Netherlands*
[d] *Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, 55905, USA*
[e] *Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, 97080 Würzburg, Germany*
[f] *Department of Pathology, Laboratory Medicine Program, University Health Network and University of Toronto, Toronto, Ontario, M5G 2M9, Canada*
[g] *Institute of Metabolism and Systems Research, University of Birmingham, B15 2TT, England, UK*
[h] *Department of Oncology, University of Turin at Molinette Hospital, Turin, Italy*
[i] *Department of Pathology, Tohoku University School of Medicine, Sendai, Japan*
[j] *Southern California Permanente Medical Group, Woodland Hills Medical Center, Woodland Hills, CA, 91364, USA*
[k] *Department of Oncology, University of Turin at San Luigi Hospital, Orbassano, Turin, Italy*
[l] *University of Sydney, Sydney, New South Wales, 2006, Australia*

☆ Disclosures: None.

* Corresponding author. Department of Pathology and Clinical Laboratories 4520D MSRB I 1150 W. Medical Center Drive Ann Arbor, MI, 48109-5602, USA.

E-mail addresses: giordano@med.umich.edu (T.J. Giordano), Daniel.Berney@bartshealth.nhs.uk (D. Berney), r.r.dekrijger@umcutrecht.nl (R.R. de Krijger), Erickson.Lori@mayo.edu (L. Erickson), fassnacht_m@ukw.de (M. Fassnacht), Ozgur.Mete2@uhn.ca (O. Mete), thomaspapathomas@nhs.net (T. Papathomas), mauro.papotti@unito.it (M. Papotti), hsasano@patholo2.med.tohoku.ac.jp (H. Sasano), Lester.D.Thompson@kp.org (L.D.R. Thompson), marco.volante@unito.it (M. Volante), affgill@med.usyd.edu.au (A.J. Gill).

https://doi.org/10.1016/j.humpath.2020.10.001

[m] *Cancer Diagnosis and Pathology Group Kolling Institute of Medical Research, Royal North Shore Hospital, St Leonards, NSW, 2065, Australia*
[n] *NSW Health Pathology, Department of Anatomical Pathology, Royal North Shore Hospital, St Leonards, NSW, 2065, Australia*

Received 28 September 2020; accepted 3 October 2020

Available online 12 October 2020

Keywords:
Checklist;
Data set;
Synoptic reporting;
Structured report;
Adrenal cortical carcinoma;
ICCR

Summay Complete resection of adrenal cortical carcinoma (ACC) with or without adjuvant therapy offers the best outcome. Recurrence is common, and in individual cases, the long-term outcome is difficult to predict, making it challenging to personalize treatment options. Current risk stratification approaches are based on clinical and conventional surgical pathology assessment. Rigorous and uniform pathological assessment may improve care for individual patients and facilitate multi-institutional collaborative studies. The International Collaboration on Cancer Reporting (ICCR) convened an expert panel to review ACC pathology reporting. Consensus recommendations were made based on the most recent literature and expert opinion. The data set comprises 23 core (required) items. The core pathological features include the following: diagnosis as per the current World Health Organization classification, specimen integrity, greatest dimension, weight, extent of invasion, architecture, percentage of lipid-rich cells, capsular invasion, lymphatic invasion, vascular invasion, atypical mitotic figures, coagulative necrosis, nuclear grade, mitotic count, Ki-67 proliferative index, margin status, lymph node status, and pathological stage. Tumors were dichotomized into low-grade (<20 mitoses per 10 mm^2) and high-grade (>20 mitoses per 10 mm^2) ones. Additional noncore elements that may be useful in individual cases included several multifactorial risk assessment systems (Weiss, modified Weiss, Lin-Weiss-Bisceglia, reticulin, Helsinki, and Armed Forces Institute of Pathology scores/algorithms). This data set is now available through the ICCR website with the hope of better standardizing pathological assessment of these relatively rare but important malignancies.

1. Introduction

Adrenal cortical carcinoma (ACC) is a relatively rare malignancy, with a reported annual incidence ranging from 0.7 to 2 per million [1,2]. There is a bimodal age distribution, with a small peak before the age of 5 years (greater in areas with a high incidence of germ line *TP53* mutation) and a second much larger peak in middle age [3,4]. Complete surgical excision is the mainstay of treatment [5,6]. However, in the majority of patients, the condition recurs, even with adjuvant therapy, which is usually based on mitotane, and the 5-year survival for patients with stage IV disease is in the order of 5−15% [7,8].

The pathological assessment of ACC resection specimens is complex [9]. Although the majority of cases, which are either metastatic or invade outside the adrenal at presentation, are diagnostically straightforward, the distinction between benign and malignant disease in organ-confined (stage I, stage II) adrenal cortical tumors may be challenging and is often based on one or more of several multiparameter scoring systems, some of which may be prone to interobserver discordance [9]. Indeed, the very existence of several *competing* systems is itself evidence of the difficulty of definitive pathological differential diagnosis and risk assessment in organ-confined disease and proof that no individual system is ideal. Clearly, an internationally accepted and uniform approach to the pathological assessment of ACC would assist risk assessment for individual patients, particularly if it recorded most of the individual components of these multiparameter systems, and may help to facilitate multinational translational research studies.

The International Collaboration on Cancer Reporting (ICCR) is a not-for-profit organization that strives to produce standardized evidence-based data sets for pathology reporting. It is sponsored by major professional bodies including the Royal College of Pathologists of Australasia and the United Kingdom, the Canadian Association of Pathologists in association with the Canadian Partnership Against Cancer, the European Society of Pathology, the College of American Pathologists, the American Society for Clinical Pathology, and the Faculty of Pathology, Royal College of Physicians of Ireland. The ICCR produces data sets with a consistent style and content, which are freely available from the ICCR website at http://www.iccr-cancer.org. In this publication, we provide a brief commentary on the development of the data set for reporting ACCs, now available at http://www.iccr-cancer.org/datasets/published-datasets/endocrine/adrenal-cortex.

Table 1 Core and noncore elements for the pathology reporting of carcinoma of the adrenal cortex.

Core	Noncore
Clinical information	Tumor dimensions
	Additional dimensions (largest tumor)
Operative procedure	Necrosis
	Extent
Specimen(s) submitted	Reticulin framework
Tumor site	Multifactorial scoring systems
Specimen integrity	Margin status
	Distance of the tumor to the closest margin
Tumor dimensions	Lymph node status
	Extranodal extension (ENE)
Tumor weight	Coexistent pathology
Histological tumor type	Ancillary studies
Extent of invasion	
Tumor architecture	
Lipid-rich cells	
Capsular invasion	
Lymphatic invasion	
Vascular invasion	
Atypical mitotic figures	
Necrosis	
Nuclear grade	
Mitotic count and histological tumor grade	
Ki-67 proliferation index	
Margin status	
Lymph node status	
Histologically confirmed distant metastases	
Pathological staging	

2. Methods

Under the chairmanship of Dr. Thomas Giordano, the ICCR convened a 12-member Dataset Authoring Committee (DAC) to critically review the published evidence and develop a draft data set, which, after open consultation and feedback, was published in December 2019.

3. Area of application

The data set was developed for the pathology reporting of resection specimens of malignant adrenal cortical tumors in both adults and children. Furthermore, the authors intended that adrenal cortical tumors of low/uncertain malignant potential should also be reported using this data set. Neuroblastoma, pheochromocytoma, sarcoma, metastases to the adrenal, and lymphoma are excluded from this data set. It should not be used for core needle or incisional biopsies.

4. Core elements

The data set includes 23 *core* elements, which are listed in Table 1. The core elements are defined as those that are essential for the clinical management, staging, or prognosis of the cancer. These elements have evidentiary support at level III-2 or higher [10] or were otherwise viewed by the DAC to represent the minimum reporting standard in clinical practice. The core elements are summarized in the following sections.

4.1. Clinical information

Relevant clinical information that should be provided includes the presence of symptoms or signs suggesting endocrine dysfunction (eg, hypertension, change in body habitus, virilization), the presence of clinical syndromes (eg, Cushing syndrome or primary aldosteronism), a history of prior malignancy, a familial predisposition to cancer (eg, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, Multiple endocrine neoplasia type 1 (MEN1), Familial adenomatous polyposis (FAP), and Lynch syndrome), the results of any previous biopsy or resection, and the details of any prior treatment.

4.2. Operative procedure, specimen(s) submitted, tumor site

The type of surgery (open versus laparoscopic and partial versus total adrenalectomy) should be recorded. Laparoscopic surgery is prone to disruption of the gland, which may cause difficulty in assessing tumor size, integrity of the capsule, and adequacy of resection. The resection of any other organs (eg, liver or kidney) and regional (para-aortic and periaortic) lymph node removal should be reported. Tumor site (laterality) is an essential data point for fully characterizing any neoplasm, although there is no evidence that it affects prognosis.

4.3. Specimen integrity

Documentation of specimen integrity is essential, especially as laparoscopic surgery is being used with increasing frequency and may lead to disruption of the tumor capsule. There are options to record the specimen as intact, mostly intact but with a disrupted capsule, or fragmented.

4.4. Tumor dimensions

The largest single dimension in any direction measured in millimeters is considered a core item. The recording of all three dimensions, although useful to determine volume, is considered optional (noncore). The greatest dimension is necessary because it is a critical component of staging, and some diagnostic systems include tumor size.

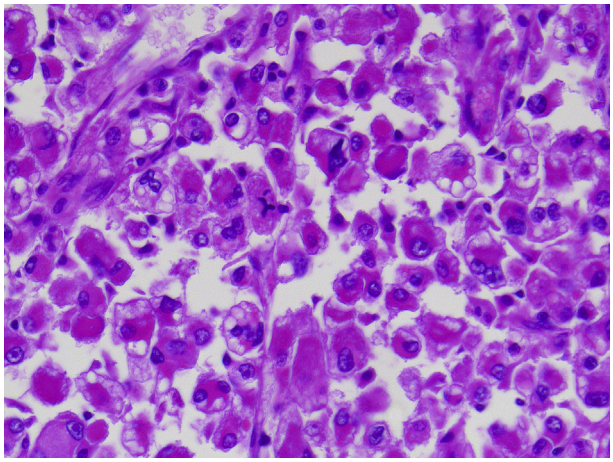

Fig. 1 Oncocytic adrenal cortical carcinoma. Oncocytic adrenal cortical carcinomas are composed of tumor cells with oncocytic change. The identification of one of the three major criteria of the Lin-Weiss-Bisceglia system justifies the diagnosis of carcinoma in *pure* oncocytic adrenal cortical neoplasms (provided by Dr. Ozgur Mete).

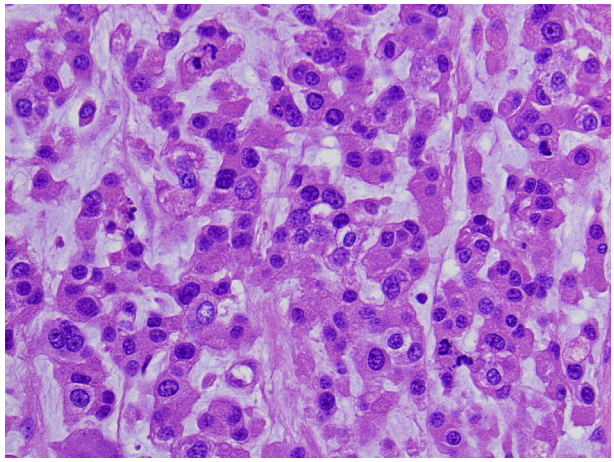

Fig. 2 Myxoid adrenal cortical carcinoma. Myxoid adrenal cortical carcinomas are distinguished with the presence of variable myxoid change in the tumor stroma (provided by Dr. Ozgur Mete).

4.5. Tumor weight

Accurate determination of tumor weight is essential for complete diagnostic assessment, and some scoring systems use tumor weight as a key element [11]. Tumor weight should be determined after other organs are removed, and adipose tissue is trimmed as much as possible without affecting the histological assessment of invasive growth.

4.6. Histological tumor type

All carcinomas of the adrenal cortex should be categorized based on the current World Health Organization (WHO) Classification of Tumors of Endocrine Organs [12]. Diagnostic categories include ACC not otherwise specified; ACC, oncocytic type (Fig. 1); ACC, myxoid type (Fig. 2); and ACC, sarcomatoid type. Adrenal cortical neoplasm of uncertain malignant potential is also a valid category for rare cases. Recognition of histological variants of ACCs is vital because some tumor types have distinct diagnostic systems. For example, oncocytic tumors are lipid-poor ones by definition and therefore should not be evaluated using the Weiss system [13,14]. Furthermore, knowledge of the morphological type can assist with future diagnostic assessments if there is recurrence.

4.7. Extent of invasion, capsular invasion

Tumor extension is pathologically distinct from tumor capsular invasion. Tumor extension is a component of pathological staging and assesses the extent of growth beyond the adrenal gland and whether the adjacent structures and organs such as the kidney, liver, and pancreas are directly involved. Almost all ACCs that involve adjacent structures are unencapsulated in the area of invasion. In contrast, almost all organ-confined ACCs are encapsulated but may show capsular invasion. There is no accepted definition of what constitutes capsular invasion, with some authorities accepting invasion into, but not through, the capsule, whereas others require full-thickness penetration [11].

4.8. Tumor architecture

In contrast to adrenal cortical adenomas, ACCs are typically characterized by diffuse tumor architecture, which is defined as solid or patternless sheets of tumor cells. Nondiffuse growth patterns include trabecular, alveolar, and nested ones. The assessment of tumor architecture is a component of many multifactorial scoring systems [15].

4.9. Lipid-rich cells

Lipid-rich cells, or clear cells, are a marker of adrenal cortical differentiation and should be recorded as $\leq$25% or $>$25% as the assessment of percentage of lipid-rich or clear cells is a component of some scoring systems, and the 25% cutoff is used by the Weiss approach [15].

4.10. Lymphatic invasion

The assessment of lymphatic (sinusoidal) invasion should be evaluated at the periphery of the tumor in, and around, the tumor capsule and not within the tumor itself. It was the opinion of the expert committee that immunohistochemical markers are usually not useful in this evaluation. The assessment of lymphatic (sinusoidal) invasion is a component of several multifactorial scoring systems.

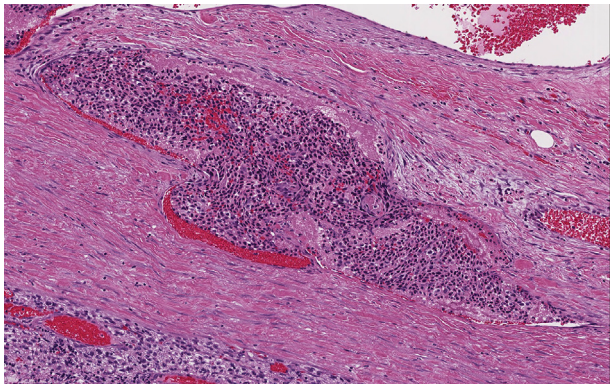

Fig. 3 Vascular invasion. Venous invasion characterized by intravascular tumor cells admixed with thrombus in the adrenal capsule (provided by Dr. Ozgur Mete).

4.11. Vascular invasion

The distinction between small-vessel invasion (capillaries) and invasion of large vessels (ie, venous) should be determined as invasion of large vessels is associated with a worse prognosis [16]. Smooth muscle in the wall is a useful adjunct to recognize large-vessel invasion. Intravascular tumor cells, admixed with thrombus, are thought to be the most reliable marker of vascular invasion with established prognostic significance (Fig. 3). The assessment of venous invasion is a component of several multifactorial scoring systems.

4.12. Atypical mitotic figures

The collective genomic studies of ACC to date indicate the presence of widespread genomic instability with significant copy number changes [17,18]. These genomic alterations can be reflected by the presence of atypical mitoses, which should be documented even when only a single unequivocal atypical mitotic figure is identified (Fig. 1). The assessment of atypical mitotic figures is a component of several multifactorial scoring systems.

4.13. Necrosis

Although it may be beneficial to distinguish between focal and extensive necrosis, there are no accepted definitions. As such, the estimation of the extent of necrosis is considered optional (noncore), but noting the presence or absence of necrosis is considered core. It is emphasized that infarct-type necrosis, degenerative-type changes with hyalinization, and hemorrhage or blood extravasation, as often seen centrally in adrenal cortical adenomas, should not be considered tumor necrosis and should be distinguished from true tumor-type (usually coagulative) necrosis—a distinction that can sometimes be difficult (Fig. 4).

4.14. Nuclear grade

Nuclear grade is a component of the Weiss multifactorial scoring system [15], using a grading system similar to the International Society of Urological Pathology (ISUP) (and older Fuhrman) criteria for renal cancer [11]. Using the Weiss criteria, the grade is assigned based on the most atypical area. A rough rule of thumb is that if nucleoli are readily visible under a 10× objective (×100 magnification), a high nuclear grade should be ascribed (Fig. 5).

4.15. Mitotic count and histological tumor grade

The mitotic count should be recorded per 10 mm^2. The literature commonly refers to mitotic count per 50 high-power fields (HPFs) without always defining the diameter of the HPFs. The estimate of 50 HPFs equating to 10 mm^2 is commonly used as this reflects many modern microscopes. However, it is emphasized that reporting pathologists must know their field diameter when calculating mitotic count and that on different microscopes, fewer or more HPFs are equivalent to 10 mm^2.

Architectural grading of ACC is not possible. Instead, tumor grade is based on tumor cell proliferation, initially determined by mitotic count and refined with the Ki-67 proliferative index. Mitotic count is essential for the diagnostic and prognostic evaluation of adrenal cortical tumors and should be reported in all cases. The mitotic count is also a component of all multifactorial scoring systems. While mitotic count is a continuous variable, one of the initial and most established mitotic grading schemes dichotomizes the count into two classes: low-grade carcinomas contain $\leq$20 mitoses per 50 HPFs (presumed to be 10 mm^2), and high-grade carcinomas contain >20 mitoses per 50 HPFs per 10 mm^2 [19]. Assessment of mitotic count is prone to reproducibility issues [20], largely owing to variation in interpretation among pathologists of what constitutes a mitotic figure and variation between microscopes without appropriate correction for different field diameters. To reduce this variation, only unequivocal mitotic figures should be counted. Pyknotic nuclei from apoptotic bodies should not be counted.

4.16. Ki-67 proliferation index

Significant evidence has accumulated that ACC is a proliferation-driven neoplasm [16–18,21], and the Ki-67 proliferation index, determined immunohistochemically using the Mib-1 antibody [22], is an important independent prognostic factor [23–26]. Assessment of the Ki-67 proliferation index should be performed on the area of tumor with the highest proliferative activity (so called *hot spots*). It is important that the Ki-67 proliferation index should be determined as accurately as possible, preferably using image analysis (Fig. 6) or manual counting if resources permit [27]. Although estimating the Ki-67 by simple

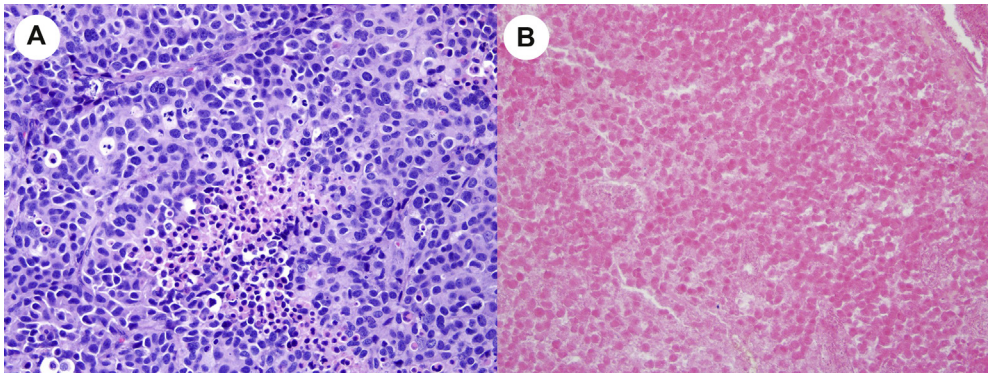

Fig. 4 Necrosis. Coagulative necrosis (A), which can be defined as a necrosis showing an abrupt transition from viable to necrotic cells without granulation or fibrous tissue, is always significant and should be distinguished from infarct-type necrosis (B), wherein the ghosted outlines of tumor cells often remain visible (provided by Dr. Thomas Giordano).

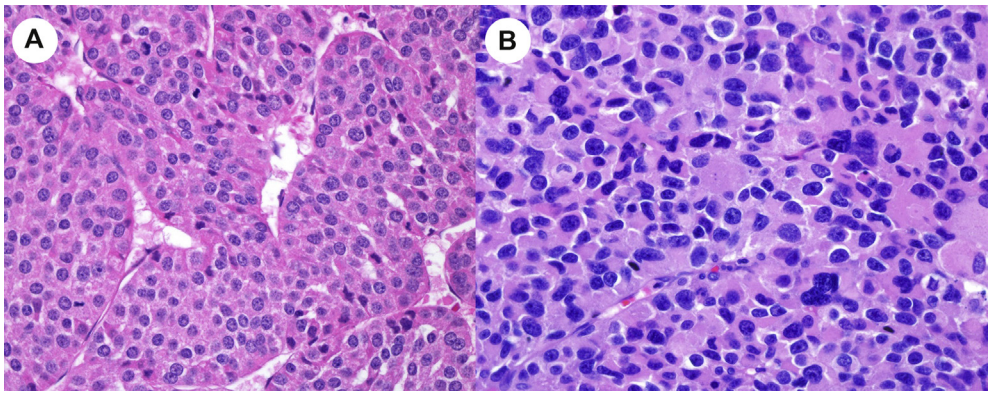

Fig. 5 Cytological atypia. The assessment of cytologic atypia may be subjective. A, When the tumor is composed of a monotonous population of relatively uniform cells lacking prominent nucleoli, the cytological atypia is considered absent. B, When there is considerable nuclear atypia usually with discernible nucleoli visible with a 10× objective, then cytological atypia is considered present (provided by Dr. Thomas Giordano).

inspection (*eyeballing*) is generally not recommended, it has been shown to have some prognostic significance and may be used when image analysis and manual counting is not possible [28]. The Ki-67 proliferative index is a continuous variable. Cutoffs to subcategorize tumors into different grades are not fully established, but some centers use a 3-tiered system based on the following cutoffs: ≤15% (low grade), >15 to ≤30 (intermediate grade), and >30% (high grade) [29]. It is hoped that the information derived from this data set may inform future practice, but until there is consensus on Ki-67 cutoffs for individual grades, the absolute Ki-67 proliferative index should be recorded.

4.17. Margin status

The presence of a clear (R0), microscopically involved (R1), or grossly transected (R2) margin is considered a core element, and large tumors should be generously sampled to adequately assess margin status. Assessment of tumor margins is essential because incomplete resection has been associated with local recurrence [30] and may be an indication for local radiation therapy [31]. In completely excised (R0) tumors, the distance to the nearest margin may provide prognostic information, but until supported by definitive evidence, the distance is considered noncore. The location of any involved margin may be difficult to accurately determine pathologically and is also considered noncore. Margin assessment may be difficult or impossible in fragmented specimens; *cannot be assessed* is often the most appropriate option in this setting.

4.18. Lymph node status

The number of lymph nodes resected and the number of those positive for malignancy are considered core elements; however, the presence or absence of extranodal extension is noncore. At this time, the size of tumor deposits has not been sufficiently well studied to be included.

4.19. Histologically confirmed distant metastases

The presence of histologically confirmed distant metastases is a critical component of pathological staging and should be recorded [32].

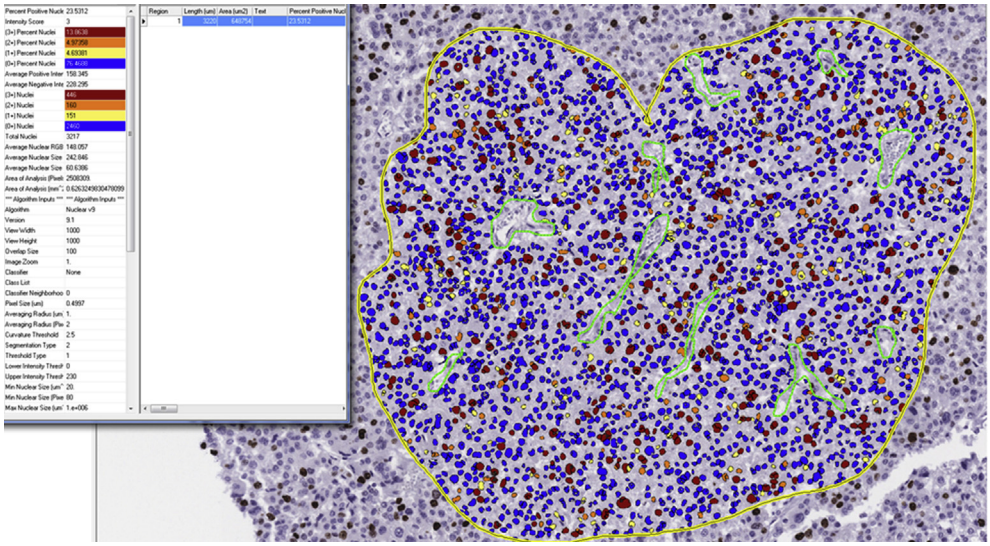

Fig. 6 Assessment of the tumor proliferation using Ki67/Mib-1. Assessment of the Ki-67 proliferation index should be performed on the area of tumor with the highest proliferative activity. Manual counting or the use of image analysis systems is strongly encouraged over eyeballing. This photomicrograph illustrates pathologist-driven automated MIB1 image analysis in a hot spot. The MIB1 labeling index is 23.53% in 3217 tumor cells (provided by Dr. Ozgur Mete).

4.20. Pathological staging

The Union for International Cancer Control has adopted the staging system proposed by the European Network for the Study of Adrenal Tumors (ENSAT), as outlined in Table 2 [33]. It is emphasized that venous tumor thrombus qualifies as pT4 disease. Although the ENSAT stage grouping is not considered mandatory, it is listed in Table 2 for reference.

Table 2 ENSAT stage groupings for adrenocortical carcinoma [33].

ENSAT stage	Definition
I	T1, N0, M0
II	T2, N0, M0
III	T1−T2, N1, M0
	T3−T4, N0−N1, M0
IV	Any T, any N, M1

NOTE. T1, tumor ≤5 cm; T2, tumor >5 cm; T3, tumor infiltration into the surrounding tissue; T4, tumor invasion into the adjacent organs or venous tumor thrombus in vena cava or renal vein; N0, no positive lymph nodes; N1, positive lymph node(s); M0, no distant metastases; M1, presence of distant metastasis.
Abbreviations: ENSAT, European Network for the Study of Adrenal Tumors.

4.21. Reticulin framework

Histochemical staining to highlight the reticulin framework is illustrated in Fig. 7. Although reticulin assessment has diagnostic utility and has been incorporated into a multiparameter algorithm [34,35], it is not needed in all cases and is therefore considered noncore.

5. Multifactorial scoring systems

Several multifactorial scoring systems have been developed for assessment of the malignant potential of adrenal cortical neoplasms. These are not always needed for diagnosis and are therefore considered noncore. As there is ongoing debate around the validation and reproducibility of these systems, the ICCR does not recommend any particular approach. Instead, the ICCR recommends that pathologists should use their judgment to select the appropriate system(s) (if any) for use in their practice for individual tumor types. The selection of the core items described previously was heavily influenced by the desire to ensure that pathologists record as consistently as possible the individual data items that contribute to the scoring systems in the hope that they may be further refined. The more commonly used systems are presented in the following sections, along with their intended uses. However, it is noted that other systems, most notably the van Slooten system [36], may be useful in specific circumstances [37].

5.1. Weiss system for conventional adrenal cortical neoplasms

The following listed are the criteria for the Weiss system [15,19]:

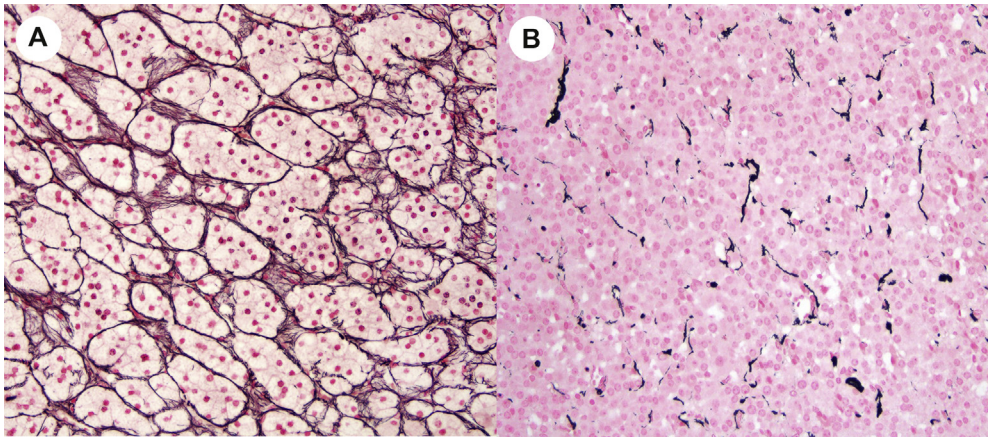

Fig. 7 Reticulin histochemistry. Assessment of reticulin histochemistry. A, When the reticulin framework is intact, reticulin surrounds individual nests of cells. B, The presence of a disrupted reticulin framework is defined by the loss of continuity of reticulin fibers across one high-power field. The original approach is that if an imaginary pathway can be drawn across a full high-power field without ever being interrupted by a reticulin boundary, then the framework is disrupted [35]. More recently, the concept of a qualitative alteration in the reticulin framework has been introduced [34] (provided by Dr. Thomas Giordano).

- High nuclear grade (yes/no)
- Mitotic count of >5 mitoses per 50 HPFs (yes/no)
- Presence of atypical mitotic figures (yes/no)
- <25% lipid-rich (clear) cells (yes/no)
- Presence of diffuse architecture (yes/no)
- Presence of tumor necrosis (yes/no)
- Presence of venous invasion (yes/no)
- Presence of lymphatic (sinusoidal) invasion (yes/no)
- Presence of capsular invasion (yes/no)

The Weiss system [15,19] can be used for the majority of conventional adrenal cortical tumors in adults, but should not be used for oncocytic tumors because they consistently display densely eosinophilic cytoplasm, a diffuse architecture, and high nuclear grade. The Weiss system consists of 9 elements, each worth one point. Tumors with Weiss scores ≥3 are considered to possess malignant potential and are considered ACCs under the current form of this system [19].

5.2. Modified Weiss system for conventional adrenal cortical neoplasms

The following listed are the criteria for the modified Weiss system [38]:

- 2 × mitotic count of >5 mitoses per 50 HPFs (yes/no)
- 2 × <25% lipid-rich (clear) cells (yes/no)
- Presence of atypical mitotic figures (yes/no)
- Presence of tumor necrosis (yes/no)
- Presence of capsular invasion (yes/no)

The modified Weiss system [38] can be also deployed for the majority of conventional adrenal cortical tumors, but should not be used for oncocytic tumors. The modified Weiss system places twice the weight on the mitotic rate and percentage of lipid-rich cells and eliminates nuclear grade, architecture, venous invasion, and lymphatic invasion. Tumors are thereby graded from 0 to 7, with those tumors scoring ≥3 possessing malignant potential. The modified Weiss system is highly correlated with the original Weiss system [38].

5.3. Lin-Weiss-Bisceglia system for oncocytic adrenal cortical neoplasms

The following are the major criteria:

- Mitotic count of >5 mitoses per 50 HPFs (yes/no)
- Presence of atypical mitotic figures (yes/no)
- Presence of venous invasion (yes/no)

The following are the minor criteria:

- Tumor size >10 cm and/or weight <200 g (yes/no)
- Presence of tumor necrosis (yes/no)
- Presence of lymphatic (sinusoidal) invasion (yes/no)
- Presence of capsular invasion (yes/no)

The Lin-Weiss-Bisceglia system [14] is used specifically for oncocytic adrenal cortical neoplasms. This system should only be applied to adrenal cortical tumors that are *purely* oncocytic. Although there are no widely accepted criteria for how much oncocytic differentiation constitutes pure differentiation, one commonly used definition requires that more than 90% of the tumor should be oncocytes [39]. Under the Lin-Weiss-Bisceglia system, pathologic features are divided into major and minor criteria. The presence of any major criterion indicates malignant potential and

connotes the diagnosis of ACC, oncocytic variant. In the absence of major criteria, the presence of any minor criterion connotes the diagnosis of an adrenal cortical neoplasm of uncertain malignant potential, oncocytic variant. If no major or minor criteria are present, the diagnosis of oncocytic adrenal cortical adenoma (*oncocytoma*) is usually appropriate (benign and therefore not reported with this data set).

5.4. Helsinki system for diagnosis and prognosis of conventional and oncocytic adrenal cortical neoplasms

The following are the criteria for the Helsinki system [40]:

- 3 × mitotic count of >5 mitoses per 50 HPFs (yes/no)
- 5 × presence of tumor necrosis (yes/no)
- Ki-67 proliferation index (percentage)

The Helsinki system [40] is a weighted tumor score combining the aforementioned three results. A Helsinki score >8.5 is associated with metastatic potential and warrants the diagnosis of ACC. The Helsinki score has been evaluated and validated for both conventional ACCs and oncocytic tumors [41].

5.5. Reticulin algorithm for the diagnosis of conventional and oncocytic adrenal cortical neoplasms

The following are the criteria for the reticulin algorithm [34,35]:

- Abnormal/absent reticulin framework (yes/no)
- Presence of tumor necrosis (yes/no)
- Mitotic rate of >5 mitoses per 50 HPFs (yes/no)
- Presence of venous invasion (yes/no)

The reticulin algorithm [34,35] uses a two-step process. First, the reticulin framework is evaluated by silver-based histochemical staining for reticulin. If disruption of the framework is observed (Fig. 7), then the tumor is evaluated for the presence of the aforementioned criteria. Tumors with both a disrupted reticulin framework and at least one of the other diagnostic criteria are considered to possess metastatic potential and can be diagnosed as ACC.

5.6. Armed Forces Institute of Pathology algorithm for pediatric adrenal cortical neoplasms

The following are the criteria for the Armed Forces Institute of Pathology (AFIP) algorithm [42]:

- Tumor weight >400 g (yes/no)
- Tumor size >10.5 cm (yes/no)

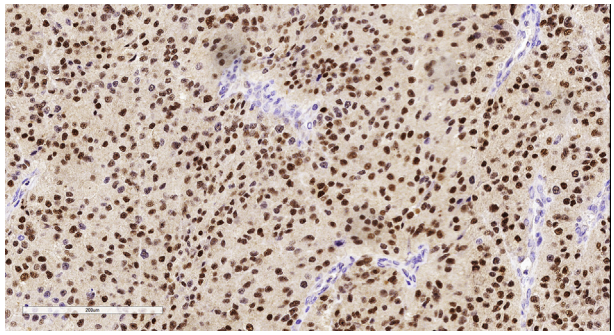

Fig. 8 Confirmation of the adrenal cortical origin. Steroidogenic factor-1 (SF-1) stands out as the most specific biomarker for the confirmation of the adrenal cortical origin of a neoplasm (provided by Dr. Ozgur Mete).

- Extra-adrenal extension (yes/no)
- Invasion into vena cava (yes/no)
- Presence of venous invasion (yes/no)
- Presence of capsular invasion (yes/no)
- Presence of tumor necrosis (yes/no)
- Mitotic count of >15 mitoses per 20 HPFs (yes/no)
- Presence of atypical mitotic figures (yes/no)

The Wieneke/AFIP algorithm from Wieneke et al [42] was developed for pediatric adrenal cortical neoplasms and reflects the observation that these tumors have a much lower risk of recurrence than their adult counterparts despite similar histologic features, which also may reflect their different genomic landscapes [43]. Although there is no clean breakpoint above or below which patients can be definitively classified as benign or malignant with complete confidence, 0 to 2 criteria are associated with a benign long-term clinical outcome; the presence of 3 criteria is considered indeterminate for malignancy (uncertain malignant potential); and four or more criteria connotes a high risk of poor outcomes and can be considered ACC. Additional efforts to include the Ki-67 proliferation index into the evaluation of pediatric tumors are ongoing [43,44].

6. Ancillary studies and other noncore elements

Increasingly, patients with ACC are undergoing significant ancillary testing. Some of these markers are immunohistochemical ones and are used to confirm primary adrenal cortical origin (eg, steroidogenic factor-1, Melan-A, calretinin) (Fig. 8) or to assist in the distinction between benign and malignant disease (eg, IGF2, P53) (Fig. 9) [45–47]. Similar to p53 overexpression, diffuse nuclear beta-catenin expression also correlates with aggressive tumor molecular clusters [48]. Phosphohistone H3 has been used by some to reduce the interobserver variability in the assessment of mitotic count [49]. Next-generation sequencing–based panel genotyping is increasingly being used.

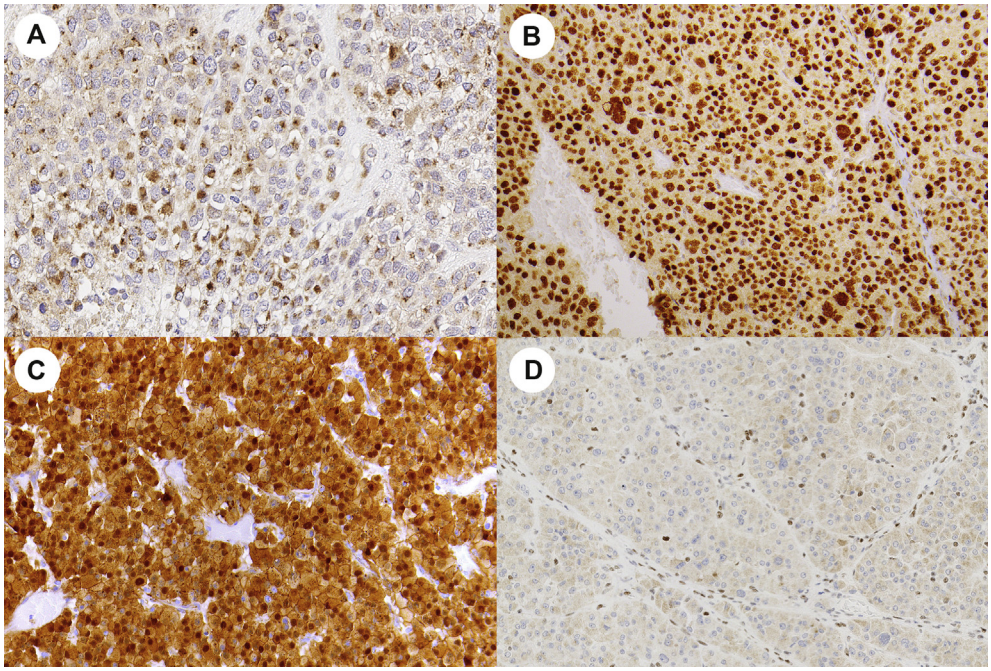

Fig. 9 Additional immunohistochemical markers. A, Positive staining for Insulin-like growth factor 2 (IGF2) supports the diagnosis of adrenal cortical carcinoma over adenoma. Characteristically, IGF2 shows paranuclear *dot-like* cytoplasmic expression or accentuation. B, P53 overexpression is useful in the distinction of carcinoma from adenoma in the appropriate clinicopathologic context. C, Nuclear beta-catenin expression is enriched in a subset of aggressive adrenal cortical carcinomas. D, Given the established link with Lynch syndrome [32,50], and the potential to guide therapy, microsatellite instability testing or mismatch repair marker (MLH1, MSH2, MSH6, and PMS2) immunohistochemistry is encouraged. The photomicrograph illustrates a MSH2-immunodeficient adrenal cortical carcinoma (provided by Dr. Ozgur Mete).

The significance of such testing should be interpreted in the general context of the specific case. Given the recent recognition that a small percentage of patients with ACC have Lynch syndrome [32,50], screening for mismatch repair protein defects by immunohistochemistry is encouraged (Fig. 9D).

7. Conclusion

The goal of the ICCR in producing the data set for ACC was to improve patient management, facilitate national and international benchmarking, and enable multicenter research through standardized data collection. It is hoped that this data set will harmonize the pathological reporting of this rare malignancy and that this commentary has provided an explanation and rationale for the core and noncore elements selected.

Acknowledgments

The authors recognize the sponsoring societies and organizations. They particularly acknowledge Fleur Webster for her exceptional organizational and editing contributions. The views expressed are solely those of the authors.

References

[1] Allolio B, Fassnacht M. Clinical review: adrenocortical carcinoma: clinical update. J Clin Endocrinol Metabol 2006;91:2027−37.
[2] Kerkhofs TM, Verhoeven RH, Van der Zwan JM, et al. Adrenocortical carcinoma: a population-based study on ncidence and survival in The Netherlands since 1993. Eur J Canc 2013;49:2579−86 (Oxford, England : 1990).
[3] Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. Endocr Rev 2014;35:282−326.
[4] Lacroix A. Approach to the patient with adrenocortical carcinoma. J Clin Endocrinol Metabol 2010;95:4812−22.
[5] Fassnacht M, Dekkers OM, Else T, et al. European society of endocrinology clinical practice guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the study of adrenal tumors. Eur J Endocrinol 2018;179:G1−g46.
[6] Fassnacht M, Assie G, Baudin E, et al. Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up(†). Ann Oncol 2020. official journal of the European Society for Medical Oncology, S0923-7534(20)42107-42116 [epub ahead of print].

[7] Berruti A, Grisanti S, Pulzer A, et al. Long-term outcomes of adjuvant mitotane therapy in patients with radically resected adrenocortical carcinoma. J Clin Endocrinol Metabol 2017;102:1358–65.
[8] Libé R, Borget I, Ronchi CL, et al. Prognostic factors in stage III-IV adrenocortical carcinomas (ACC): an European Network for the Study of Adrenal Tumor (ENSAT) study. Ann Oncol 2015;26:2119–25. official journal of the European Society for Medical Oncology.
[9] Fassnacht M, Kroiss M, Allolio B. Update in adrenocortical carcinoma. J Clin Endocrinol Metabol 2013;98:4551–64.
[10] Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence. BMC Med Res Methodol 2009;9:34.
[11] Giordano T, Chrousos G, de Krijger R, et al. Adrenal cortical carcinoma. In: Lloyd R, Osamura R, Klöppel G, Rosai J, editors. WHO classification of tumours of endocrine organs. 4th ed. Lyon: IARC Press; 2017.
[12] Lloyd R, Osamura R, Klöppel G, Rosai J. WHO classification of tumours of endocrine organs. 4th ed. Lyon: IARC Press; 2017.
[13] Lau SK, Weiss LM. The Weiss system for evaluating adrenocortical neoplasms: 25 years later. Hum Pathol 2009;40:757–68.
[14] Bisceglia M, Ludovico O, Di Mattia A, et al. Adrenocortical oncocytic tumors: report of 10 cases and review of the literature. Int J Surg Pathol 2004;12:231–43.
[15] Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol 1984;8:163–9.
[16] Mete O, Gucer H, Kefeli M, Asa SL. Diagnostic and prognostic biomarkers of adrenal cortical carcinoma. Am J Surg Pathol 2018;42:201–13.
[17] Assie G, Letouze E, Fassnacht M, et al. Integrated genomic characterization of adrenocortical carcinoma. Nat Genet 2014;46:607–12.
[18] Zheng S, Cherniack AD, Dewal N, et al. Comprehensive pangenomic characterization of adrenocortical carcinoma. Canc Cell 2016;29:723–36.
[19] Weiss LM, Medeiros LJ, Vickery Jr AL. Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol 1989;13:202–6.
[20] Yigit N, Gunal A, Kucukodaci Z, Karslioglu Y, Onguru O, Ozcan A. Are we counting mitoses correctly? Ann Diagn Pathol 2013;17:536–9.
[21] Giordano TJ, Kuick R, Else T, et al. Molecular classification and prognostication of adrenocortical tumors by transcriptome profiling. Clin Canc Res 2009;15:668–76.
[22] Gerdes J. Ki-67 and other proliferation markers useful for immunohistological diagnostic and prognostic evaluations in human malignancies. Semin Canc Biol 1990;1:199–206.
[23] Beuschlein F, Weigel J, Saeger W, et al. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. J Clin Endocrinol Metabol 2015;100:841–9.
[24] Duregon E, Molinaro L, Volante M, et al. Comparative diagnostic and prognostic performances of the hematoxylin-eosin and phosphohistone H3 mitotic count and Ki-67 index in adrenocortical carcinoma. Mod Pathol 2014;27:1246–54. an official journal of the United States and Canadian Academy of Pathology, Inc.
[25] Morimoto R, Satoh F, Murakami O, et al. Immunohistochemistry of a proliferation marker Ki67/MIB1 in adrenocortical carcinomas: Ki67/MIB1 labeling index is a predictor for recurrence of adrenocortical carcinomas. Endocr J 2008;55:49–55.
[26] Renaudin K, Smati S, Wargny M, et al. Clinicopathological description of 43 oncocytic adrenocortical tumors: importance of Ki-67 in histoprognostic evaluation. Mod Pathol 2018;31:1708–16.
[27] Lu H, Papathomas TG, van Zessen D, et al. Automated Selection of Hotspots (ASH): enhanced automated segmentation and adaptive step finding for Ki67 hotspot detection in adrenal cortical cancer. Diagn Pathol 2014;9:216.
[28] Yamazaki Y, Nakamura Y, Shibahara Y, et al. Comparison of the methods for measuring the Ki-67 labeling index in adrenocortical carcinoma: manual versus digital image analysis. Hum Pathol 2016;53:41–50.
[29] Papathomas TG, Pucci E, Giordano TJ, et al. An international Ki67 reproducibility study in adrenal cortical carcinoma. Am J Surg Pathol 2016;40:569–76.
[30] Glenn JA, Else T, Hughes DT, et al. Longitudinal patterns of recurrence in patients with adrenocortical carcinoma. Surgery 2019;165:186–95.
[31] Sabolch A, Else T, Griffith KA, et al. Adjuvant radiation therapy improves local control after surgical resection in patients with localized adrenocortical carcinoma. Int J Radiat Oncol Biol Phys 2015;92:252–9.
[32] Raymond VM, Everett JN, Furtado LV, et al. Adrenocortical carcinoma is a lynch syndrome-associated cancer. J Clin Oncol 2013;31:3012–8. official journal of the American Society of Clinical Oncology.
[33] Fassnacht M, Johanssen S, Quinkler M, et al. Limited prognostic value of the 2004 International Union against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. Cancer 2009;115:243–50.
[34] Duregon E, Fassina A, Volante M, et al. The reticulin algorithm for adrenocortical tumor diagnosis: a multicentric validation study on 245 unpublished cases. Am J Surg Pathol 2013;37:1433–40.
[35] Volante M, Bollito E, Sperone P, et al. Clinicopathological study of a series of 92 adrenocortical carcinomas: from a proposal of simplified diagnostic algorithm to prognostic stratification. Histopathology 2009;55:535–43.
[36] van Slooten H, Schaberg A, Smeenk D, Moolenaar AJ. Morphologic characteristics of benign and malignant adrenocortical tumors. Cancer 1985;55:766–73.
[37] van't Sant HP, Bouvy ND, Kazemier G, et al. The prognostic value of two different histopathological scoring systems for adrenocortical carcinomas. Histopathology 2007;51:239–45.
[38] Aubert S, Wacrenier A, Leroy X, et al. Weiss system revisited: a clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. Am J Surg Pathol 2002;26:1612–9.
[39] Bisceglia M, Ben-Dor D, Pasquinelli G. Oncocytic adrenocortical tumors. Pathol Case Rev 2005;10:228–42.
[40] Pennanen M, Heiskanen I, Sane T, et al. Helsinki score-a novel model for prediction of metastases in adrenocortical carcinomas. Hum Pathol 2015;46:404–10.
[41] Duregon E, Cappellesso R, Maffeis V, et al. Validation of the prognostic role of the "Helsinki Score" in 225 cases of adrenocortical carcinoma. Hum Pathol 2017;62:1–7.
[42] Wieneke JA, Thompson LD, Heffess CS. Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. Am J Surg Pathol 2003;27:867–81.
[43] Pinto EM, Chen X, Easton J, et al. Genomic landscape of paediatric adrenocortical tumours. Nat Commun 2015;6:6302.
[44] Picard C, Orbach D, Carton M, et al. Revisiting the role of the pathological grading in pediatric adrenal cortical tumors: results from a national cohort study with pathological review. Mod Pathol 2019;32:546–59.
[45] Soon PS, Gill AJ, Benn DE, et al. Microarray gene expression and immunohistochemistry analyses of adrenocortical tumors identify IGF2 and Ki-67 as useful in differentiating carcinomas from adenomas. Endocr Relat Canc 2009;16:573–83.
[46] Creemers SG, van Koetsveld PM, van Kemenade FJ, et al. Methylation of IGF2 regulatory regions to diagnose adrenocortical carcinomas. Endocr Relat Canc 2016;23:727–37.

[47] Mete O, Asa SL, Giordano TJ, Papotti M, Sasano H, Volante M. Immunohistochemical biomarkers of adrenal cortical neoplasms. Endocr Pathol 2018;29:137–49.

[48] Ragazzon B, Libé R, Gaujoux S, et al. Transcriptome analysis reveals that p53 and {beta}-catenin alterations occur in a group of aggressive adrenocortical cancers. Canc Res 2010;70:8276–81.

[49] Voss SM, Riley MP, Lokhandwala PM, Wang M, Yang Z. Mitotic count by phosphohistone H3 immunohistochemical staining predicts survival and improves interobserver reproducibility in well-differentiated neuroendocrine tumors of the pancreas. Am J Surg Pathol 2015;39:13–24.

[50] Challis BG, Kandasamy N, Powlson AS, et al. Familial adrenocortical carcinoma in association with lynch syndrome. J Clin Endocrinol Metabol 2016;101:2269–72.