REVIEW

Advances in adrenal tumors 2018

J Crona¹, F Beuschlein²,³, K Pacak⁴ and B Skogseid¹

¹Department of Medical Sciences, Uppsala University, Uppsala, Sweden
²Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany
³Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, UniversitätsSpital Zürich, Zürich, Switzerland
⁴Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health & Human Development, National Institutes of Health, Bethesda, Maryland, USA

Correspondence should be addressed to J Crona: joakim.crona@medsci.uu.se

Abstract

This review aims to provide clinicians and researchers with a condensed update on the most important studies in the field during 2017. We present the academic output measured by active clinical trials and peer-reviewed published manuscripts. The most important and contributory manuscripts were summarized for each diagnostic entity, with a particular focus on manuscripts that describe translational research that have the potential to improve clinical care. Finally, we highlight the importance of collaborations in adrenal tumor research, which allowed for these recent advances and provide structures for future success in this scientific field.

Introduction

Clinically unapparent adrenal tumors are found in 2–10% of the population worldwide. Cases that do require treatment are enriched in risk populations particularly those with hypertension or genetic risk factors (overview in Fassnacht et al. 2016, Young et al. 2017). Those that are associated with endocrine disturbances can cause severe patient morbidity and remains difficult to recognize and diagnose. Metastatic disease is a rare but lethal condition that can only be cured through complete surgical resection. Thus, in order to improve outcomes from adrenal tumor disease, there is a clear need for improved diagnostic methods, prognostic and predictive biomarkers but most importantly for improved therapeutic strategies.

Here, we performed a systematic review of research papers with an electronic publication date during 2017 and that were focused on adrenal tumors. A total of 349 papers including basic science and clinical studies were identified – 154 on pheochromocytomas (PCCs) and paragangliomas (PGLs, collectively denoted PPGLs), 177 on adrenocortical tumors and 18 that fell into a general adrenal tumor category. In this review, we have referenced 110 of these manuscripts and selected three prominent topics that we felt deserved special attention (Table 1).

Key Words
- pheochromocytoma
- paraganglioma
- adrenocortical carcinoma
- adrenocortical adenoma
- adrenal tumor

Two placebo-controlled clinical trials for adrenal tumors (FIRSTMAPP and ADIUVO) were both initiated and...
executed through members of ENSAT. NIH and A5 were both associated with six clinical trials each. Guidelines relevant to adrenal tumor patients are summarized in Table 4.

### Development and molecular characterization of the adrenal gland

Del Valle et al. studied adrenogonadal development during weeks 6–10 and characterized the processes of testis determination, onset of steroidogenesis and primordial germ cell development. Their genomic atlas of human adrenal and gonad development proposed new candidate genes for adrenal and reproductive disorders (Del Valle et al. 2017). The adrenal medulla is thought to originate from cells of the neural crest. Furlan et al. provided further evidence that multipotent peripheral glial cells also generate neuroendocrine cells of the adrenal medulla (Furlan et al. 2017).

The Human Protein Atlas (https://www.proteinatlas.org) aims to map all the human proteins in cells, tissues and organs using integration of various omics technologies. It has employed more than 26,000 antibodies on multiple tissues, cells and pathological states. The consortium now presented their data on the adrenal gland with RNA sequencing of tissue homogenates that identified 253 genes with an elevated expression pattern compared to other tissues (Bergman et al. 2017). Spatial expression patterns of the translated proteins were studied using immunohistochemistry.

### Incidentally discovered adrenal tumors

Clinical practice guidelines issued by the European Society of Endocrinology and ENSAT provide 19 recommendations, 16 of which are based on very low-quality evidence and 3 on low-quality evidence. The recommendations assert that adrenal tumors <4 cm...
with imaging characteristics of \( \leq 10 \) Hounsfield units do not require further follow-up imaging. Recently, these data were now confirmed by a retrospective follow-up study (Hong et al. 2017). Conflicting data state that, for such patients, one-time follow-up evaluation involving a noncontrast CT and biochemical evaluation is cost-effective (Chomsky-Higgins et al. 2018).

For intermediate lesions, there is an increasing amount of data that \(^{18}\)F-fluorodeoxyglucose (FDG) PET/CT could improve diagnosis (Altinmakas et al. 2017, Delivanis et al. 2018). A prospective study showed that \(^{18}\)F-FDG PET/CT complements adrenal washout CT in the evaluation of adrenal masses with 86.7% sensitivity and 86.1% specificity for the detection of adrenocortical carcinoma (ACC) (Guerin et al. 2017). Finally, computational analysis of images data represents another venue to improve classification of adrenal tumors; Chai et al. performed a retrospective experiment where they reached a 90% accuracy analyzing 436 CT scans (Chai et al. 2017). Although prospective studies are lacking, we expect this field to evolve fast.

### PCC and PGL

Our synthesis of the advances in PPGL is provided in Fig. 1.

### Clinical studies

#### Classifications

The World Health Organization has released updated classifications of tumors from endocrine organs as well as the head and neck region. PPGLs are now

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**Table 3** Recruiting clinical trials for adrenal cortical tumors.

| Intervention                  | Design                                      | Setting            | Recruitment target, n patients | NCT number     |
|------------------------------|---------------------------------------------|--------------------|--------------------------------|----------------|
| Randomized                   |                                             |                    |                                |                |
| Mitotane                     | Phase III                                   | Adjuvant           | 200                            | NCT00777244    |
| ATR-101                      | Phase II, placebo controlled                | Palliative (symptom reduction) | 16                | NCT03053271    |
| Surgery + medical therapy vs medical therapy | Randomized study                          | Curative           | 110                            | NCT02364089    |
| Non-randomized               |                                             |                    |                                |                |
| RF-ablation                  | Single-arm study                            | Curative           | 25                             | NCT02756754    |
| Pembrolizumab                | Phase II, single arm                        | Palliative         | 39                             | NCT02673333    |
| Studies investigating multiple diseases | Phase I, single arm, basket                  | Palliative         | 100                            | NCT03145909    |
| ABBV-176                     | Phase II, single arm                        | Palliative         | 110                            | NCT02867592    |
| Cabozantinib-S-malate        | Phase II, single arm                        | Palliative         | 57                             | NCT03333616    |
| Nivolumab and ipilimumab    | Phase II, single arm                        | Palliative         | 707                            | NCT02834013    |
| Nivolumab and ipilimumab    | Phase II, single arm                        | Palliative         | 250                            | NCT02721732    |

NCT, ClinicalTrials.gov registry number; RF, Radiofrequency.

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**Table 4** Guidelines on adrenal tumors.

| Topic                                      | Year | Organization       | Reference            |
|--------------------------------------------|------|--------------------|----------------------|
| Published during 2017                      |      |                    |                      |
| Adrenal incidentalomas, diagnosis          | 2017 | ACR                | Mayo-Smith et al. (2017) |
| PPGL, surveillance recommendations         | 2017 | Consensus Committee| Rednam et al. (2017)  |
| PPGL, genetic diagnosis and NGS            | 2017 | Consensus Committee| Toledo et al. (2017)  |
| ACC, surgery                               | 2017 | ESES & ENSAT       | Gaujoux & Mihai (2017) |
| Published earlier than 2017                |      |                    |                      |
| Adrenal incidentalomas, diagnosis          | 2016 | ENSAT              | Fassnacht et al. (2016) |
| PPGL, management                           | 2014 | Endocrine Society  | Lenders et al. (2014) |
| PPGL, follow-up                            | 2016 | ESE                | Plouin et al. (2016)  |
| Primary aldosteronism, management          | 2016 | Endocrine Society  | Funder et al. (2016)  |
| Cushing syndrome, diagnosis                | 2008 | Endocrine Society  | Nieman et al. (2008)  |
| Cushing syndrome, treatment                | 2015 | Endocrine Society  | Nieman et al. (2015)  |

ACC, adrenocortical carcinoma; ACR, American College of Radiology; ENSAT, European Network for the Study of Adrenal Tumors; ESE, European Society of Endocrinology; ESES, European Society of Endocrine Surgeons; NGS, next-generation sequencing; PPGL, pheochromocytoma and paraganglioma.
classified as PCCs, sympathetic PGLs or head and neck (parasympathetic) PGLs (Lam 2017, Lloyd et al. 2017, Williams & Tischler 2017). Both classifications highlight the hereditary nature of PPGLs and emphasize that they ‘remain tumors of undetermined biologic potential and should not be termed benign’. This classification has been complemented by the first TNM staging system for PPGL released by the American Joint Committee on Cancer (Jimenez et al. 2017, Roman-Gonzalez & Jimenez 2017).

Disease outcomes

Outcome from catecholamine excess

A study using the Nationwide Inpatient Sample studied outcomes after unilateral adrenalectomy among patient with hormonally active tumors (n = 6033), those with PCCs had a higher rate of comorbidities including congestive heart failure, chronic lung disease and malignant hypertension (Parikh et al. 2017). A systematic review identified 163 occurrences of PCCs and cardiomyopathy (Zhang et al. 2017). Hypertension was the presenting symptom in 65% and the classic triad of headache, palpitations and diaphoresis was observed in only 4%.

PCC resection led to improvement of cardiomyopathy in 96% of patients, while lack of resection was associated with death or cardiac transplantation in 44% patients. Majtan et al. performed a prospective study on the effects of surgical resection on carotid intima-media thickness and left ventricular mass in 50 PPGL patients (Majtan et al. 2017). Both parameters significantly regressed after tumor removal; in contrast to patients with essential hypertension.

Outcome from metastatic disease

A meta-analysis on outcomes of patients with metastatic PPGLs showed a 5-year survival rate of 63% (95% CI, 49–76%) with poor survival associated with male sex and synchronous metastases (Hamidi et al. 2017a). The authors also describe the natural course of metastatic PPGLs at their referral center (Hamidi et al. 2017b). Among 272 patients, the median overall survival was 24.6 years. On the other hand, a subset of patients had a very aggressive disease course of the disease. This remarkably variability in patients affected by metastatic PPGL is supported by the authors’ own experience.

Prospective clinical trials

High-specific activity

I-131 meta-iodobenzylguanidine

In a phase 1 study, safety and efficacy of this compound was investigated in 21 metastatic PPGLs (Noto et al. 2018). The maximum tolerated dose was determined and the majority (84%) of adverse events were considered mild or moderate in severity. A 19% response rate on anatomical imaging was reported, only patients who received >18.5 GBq of study drug had a response.

Pazopanib

This phase II trial for advanced/progressive metastatic PPGL was halted due to poor accrual (Jasim et al. 2017). One of six patients had a partial response (duration 2.4 years). The authors stress that optimal alpha- and beta-adrenoceptor blockade is important in patients with secretory tumors to avoid risk of potentially life-threatening complications.

Retrospective studies

Surgical treatment

In 53 PPGLs with synchronous metastases, patients with surgical resection of the primary tumor have a longer
Advances in adrenal tumors

Rijken
Tufton
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Overall survival than those who did not (85 months vs 36 months) (Roman-Gonzalez et al. 2017). A second study investigated perioperative complications in 110 patients with and 166 without alpha-adrenoceptor blockade (Groeben et al. 2017). There was no difference in the incidence of excessive hypertensive episodes between the groups and no major complications occurred. The authors concluded that ‘the basis for the general recommendation of perioperative α-receptor blockade for PCC surgery demands further study’. A commentary stated that ‘when considering abandoning this conventional therapy altogether, one needs to carefully consider the confidence regarding the safety of this revised approach’ (Grocott 2017). In addition, this study does not consider preoperative safety that is of concern in patients with catecholamine-secreting tumors.

Oncological treatment
Efficacy and safety of peptide receptor radionuclide therapy (PRRT) (Kong et al. 2017), in combination with 131I-meta-iodobenzylguanidine (MIBG) (Nastos et al. 2017), interferon-alpha (Hadoux et al. 2017), and cyclophosphamide, vincristine and dacarbazine (CVD) were reported from retrospective materials. SDHB patients had a higher response rate to CVD compared to those without SDHB mutations (Asai et al. 2017, Fishbein et al. 2017a).

Translating molecular findings to the clinic
Disease penetrance and surveillance of gene carriers
Mutations in succinate dehydrogenase subunits A–D (SDHx) were thought to have almost complete penetrance for PPGl. This figure has now been adjusted, a finding of major importance when designing surveillance protocols for healthy carriers: the overall penetrance of SDHB mutations was estimated to be 21% at the age of 50 years and 42% at the age of 70 years (Rijken et al. 2018). A second study showed a penetrance of 49.8% at 85 years (Jochmanova et al. 2017). Penetration of any SDHA-related manifestation in non-index patients was 13% at age 40 years (Bausch et al. 2017) and 10% at the age of 70 years (van der Tuin et al. 2018). The clinical spectrum associated with hereditary leiomyomatosis and renal cell carcinoma syndrome (associated with FH mutations) was assessed in 182 cases from 114 families and found only two cases of PPGl (Muller et al. 2017).

These findings align with a calculation of the optimal surveillance for head and neck PGL in SDHB mutation carriers; it has been suggested to start at the age of 27 with an interval of 3.2 years (Eijkelenkamp et al. 2017). The second study reported outcomes of annual surveillance imaging in SDHB mutation carriers (Tufton et al. 2017): in 27 index patients, 51 PPGls (five metachronous) were detected. SDHB-related tumors occurred in 25% of asymptomatic carriers on surveillance screening: ten on the first surveillance imaging and five on subsequent imaging 2–6 years later. The authors suggested the use of annual or biannual imaging with MRI. These intervals are in line with recommendations on surveillance in childhood for some hereditary PPGls (Rednam et al. 2017).

Evaluation and treatment
Functional imaging
It is now established that the most optimal tracer for PET imaging can be selected from an underlying driver mutation. This knowledge was further refined in patients with polycythemia/PGL syndrome, optimal tracers being 18F-dihydroxyphenylalanine and 18F-fluorodopamine as well as pediatric SDHx-associated PPGl, optimal tracer being 68Ga-tetraazacyclododecane tetraacetic acid–octreotate (DOTATATE) (Janssen et al. 2017, Jha et al. 2017). Previous results also showed superiority of 68Ga-DOTATATE for detection of SDHB-related metastatic PPGl as well as PGLs of the head and neck (Janssen et al. 2015, Janssen et al. 2016). We believe that these findings will lead to a change in golden standard for staging and localization of PPGl from 18F-FDGPET to a precision medicine-based approach. The norepinephrine transporter has a long-standing tradition as a target for 123I-MIBG scintigraphy, that has inborn limitations related to the imaging technology. Pandit-Taskar et al. described a PET analog, 18F-meta-fluorobenzylguanidine, that was safe, had favorable biodistribution and with good targeting of tumors (Pandit-Taskar et al. 2018).

Surgery
Preoperative genetic testing of PPGls was found to influence the surgical approach and the extent of adrenal surgery (Nockel et al. 2018). Those with RET, VHL or NF1 germline mutations more often had minimally invasive surgery with cortical-sparing adrenalectomy, whereas seven out of eight (87.5%) patients with SDHB mutation had an open approach. The underlying argument was to preserve cortical function in patients with a high risk of bilateral PCC having a low risk of metastatic disease.
(RET and VHL carriers), whereas those with a low risk of bilateral PPC but with risk factors for metastases (including SDHB and large tumor size) could benefit from an open approach to maximize probability of radical resection. A second study show that patients with NF type 1 had more volatile intraoperative course and more severe complications, probably related to larger tumors and abundant catecholamine secretion that resulted in a high proportion of open resections (Butz et al. 2017).

Pathology
Koh et al. evaluated grading systems for predicting metastatic potential in PPGLs: they validated the grading system for PPGL (GAPP) and proposed a modified GAPP with addition of SDHB staining to be useful for the prediction of the metastatic potential and prognosis in PPGL (Koh et al. 2017).

Translational research and basic science
Molecular atlas of PPGL: the Cancer Genome Atlas study
The Cancer Genome Atlas described results from 173 PPGLs that were analyzed with six different molecular profiling technologies, the most comprehensive molecular characterization of PPGL ever performed (Fishbein et al. 2017b). All data are freely available online (https://gdc.cancer.gov) and serves to accelerate research in this rare entity. Disease-causing mutations or gene fusions occurred in 73% of cases. At least two novel disease-causing genes were identified: MAML3 and CSDE1. Integrated analysis classified PPGL into three main subtypes: kinase signaling, pseudohypoxia and Wnt altered. A forth subtype, cortical admixture, was also detected but is thought to reflect a signal from non-tumoral cells.

Data from The Cancer Genome Atlas (TCGA) have already allowed PPGL to be included into several pan-cancer analyses; the first underscore that PPGL genomes exhibit relatively low number of somatic mutations as well as copy number segmentations compared to other tumors (Cancer Genome Atlas Network 2017). The second study investigated patterns of selection in cancer and confirmed known PPGL drivers as subjected to positive selection (Martincorena et al. 2017). Smaller studies complement the TCGA effort by demonstrating activating FGFR1 mutations (Welander et al. 2018) as well as different landscapes of aneuploidy in SDHB versus SDHAF2, SDHD and VHL-related cases (Hoekstra et al. 2017). One aspect that TCGA did not cover was tumor evolution. Flynn et al. reported data from sequencing of tumors from syndromic patients with multiple PPGLs, different tumors shared rare somatic copy number suggesting that these changes could have been acquired early within common precursor cells (Flynn et al. 2017).

A third pan-cancer study performed a systematic analysis of telomere length, PPGLs were found to be exceptional as it lacks both telomerase reverse transcriptase (TERT) expression and mechanisms of alternative lengthening of telomeres in the highest proportion of cases (Barthel et al. 2017). Two mechanisms underlying increased TERT expression were identified: TERT structural rearrangements (D'Antongiovanni et al. 2018) and TERT promoter hypermethylation (Svahn et al. 2018). These molecular data have allowed the stratification of PPGLs into subgroups have distinct molecular–biochemical–imaging signatures (reviewed in Crona et al. 2017).

New treatment candidates and tumor models
Lack of representative tumor models has impeded progress toward new therapeutics for PPGLs. This year, patient-derived xenografts in NOD SCID gamma mice (Powers et al. 2017) as well as SDHB-silenced mouse PCC spheroids (D’Antongiovanni et al. 2017) were described and could potentially fill this gap. Effect of the following agents was suggested: HSP90 inhibitor (NVP-AUY922) in PC12 cells (Lian et al. 2017), anthracyclines through inhibition of the hypoxia signaling pathway in mouse PCC cell lines (Pang et al. 2017) and proteasome inhibitor (Bortezomib) in mouse PCC cell lines (Bulova et al. 2017). Rapalogues is approved for treatment for gastrointestinal neuroendocrine tumors but its efficacy in PPGLs has been doubted. This may have to be re-challenged as the mTORC1 complex was found to be overactivated in PPGL both of the head and neck and those harboring SDHx mutations (Oudijk et al. 2017).

Adrenocortical tumors
Our synthesis of the advances in adrenocortical tumors is provided in Fig. 2.

Improved diagnosis
The 2017 World Health Organization classification recognizes Weiss score as the primary determinant of malignancy of adrenocortical tumors (Lam 2017, Lloyd et al. 2017). Three rare subtypes of ACC are recognized – oncocytic, myxoid and sarcomatoid
carcinomas. Clinical and biochemical features together with absence of malignant criteria are used to diagnose adrenocortical adenoma (ACA). Thus, improved methods for subclassification of adrenocortical tumors are sought for: in three independent studies, the authors showed that different adrenal disorders have unique metabolic fingerprints that can be detected in serum or urine through mass spectrometry (Hines et al. 2017, Patel et al. 2017, Taylor et al. 2017). The aldosterone-to-renin ratio was evaluated prospectively for detection of aldosterone-producing adenoma (APA); baseline and post-captopril aldosterone-renin ratio showed similar diagnostic accuracy in both the exploratory and validation cohorts, indicating lack of diagnostic gain with this confirmatory test (Maiolino et al. 2017). Radiographically identified adrenal nodules are not always a source of primary aldosteronism (PA), even when ipsilateral lateralization on adrenal vein sampling occurs (Nanba et al. 2017). One alternative could be targeting CXC chemokine receptor type 4 for functional imaging classification of both APA (Heinze et al. 2018) and ACC (Wu et al. 2017).

### Adrenocortical adenoma

**Outcomes**

A prospective study determined the prevalence of PA among 1672 primary care patients with hypertension: 5.9% had PA and one-third of these had a unilateral APA accordingly to adrenal CT scanning and adrenal vein sampling (Monticone et al. 2017). A meta-analysis of 3838 patients with PA revealed an increased risk of stroke (OR 2.58, 95% CI 1.93–3.45), coronary artery disease (1.77, 1.10–2.83), atrial fibrillation (3.52, 2.06–5.99) and heart failure (2.05, 1.11–3.78) compared to patients with essential hypertension (Monticone et al. 2018). Patients with PA were also shown to have deteriorated bone quality without loss of overall bone mass (Kim et al. 2018).

Data from the randomized SPARTACUS trial was used to study quality of life in PA patients: 1 year post adrenalectomy, quality of life normalized, whereas for patients on medical treatment, quality of life had improved but was inferior to the level of the general population (Velema et al. 2018).

### Cortisol secretion: utility in multiple scenarios

Arlt et al. analyzed steroid metabolome in 174 newly diagnosed patients with PA (103 APA, 71 bilateral adrenal hyperplasia) (Arlt et al. 2017). Patients with PA had significantly increased cortisol and total glucocorticoid metabolite excretion, only exceeded by glucocorticoid output in patients with clinically overt adrenal Cushing syndrome. In a second series, 4/5 APAs with concurrent subclinical cortisol hypersecretion were found to be composed of zona fasciculata-like cells, with heterogenous CYP11B1 and CYP11B2 immunostaining and lacking driver mutations associated with APA (Fallo et al. 2017).

Two studies confirmed the association between non-functional ACA with autonomous cortisol secretion to cardiovascular disease (Arruda et al. 2017) as well as increased mortality (Patrova et al. 2017). This was corroborated in a third study that suggested increased visceral fat as an explanation (Yener et al. 2017).

Finally, perioperative ACTH, steroid precursors and tumor size was found to predict recurrence of Cushing’s disease (El Asmar et al. 2018).

### Translating molecular findings to the clinic: new treatment options

Molecular characterization of APA has pinpointed key disease driving mechanisms that are now exploited...
by researchers as biomarkers and therapeutic targets (reviewed in Zennaro et al. 2017).

**Surgical therapy**

Kitamoto et al. correlated outcome to somatic mutation status among 142 patients with APA; KCNJ5 mutations in young patients with APA emerged as a prognostic biomarker indicating resolution of hypertension (Kitamoto et al. 2018). A second study found that CTNNB1-mutated APA had a higher possibility of residual hypertension (Wu et al. 2017).

**Medical therapy**

Following the discovery of somatic mutations in KCNJ5 (potassium channel) as a driver of APA, macrolides were shown to selectively inhibit mutant KCNJ5 opening, which might provide the option for improved diagnosis and treatment (Caroccia et al. 2017, Scholl et al. 2017). Other potential therapeutic targets of PA included the E3 ubiquitin ligase Siah1 (Scortegagna et al. 2017), neurofilament medium polypeptide (Maniero et al. 2017) and calneuron 1 (Kobuke et al. 2018).

**Translational research and basic science**

**APA**

Biology and clinicopathological characteristics of this disorder are dependent on the mutational status, an expanding field that came up with several clarifying publications (Murakami et al. 2017, Tan et al. 2017). However, whether PA is the consequence of a monoclonal or multiclonal processes is still not clear. Aging was found to correlate with remodeling of the adrenal cortex and emergence of subcapsular aldosterone-producing cell clusters (APCCs) that replaced the continuous zona glomerulosa layer. In a first study, the authors provided evidence that PA involves polyclonal APAs (Omata et al. 2017b). A second study studied 107 unilateral adrenal glands obtained from autopsies of nonhypertensive patients. Sixty-one APCCs were detected (average of 0.6 APCCs per gland) (Omata et al. 2017a). In a third study, PA patients with negative cross-sectional imaging, the resected adrenal gland showed that 13 had multiple adrenocortical micronodules and 12 had diffuse hyperplasia of zona glomerulosa based upon histopathological evaluation and CYP11B2 IHC. Aldosterone-driver gene somatic mutations were detected in 21 of 26 (81%) of CYP11B2-positive cortical micronodules (Yamazaki et al. 2017). Finally, a study reported six patients with possible APCC-to-APA transitional lesions (Nishimoto et al. 2017). These data questions if the current classification that recognizes either unilateral APA or bilateral hyperplasia is relevant especially as future personalized treatment options might be based on molecular findings rather than tumor size.

**Cortisol-producing adenoma**

Protein kinase A catalytic alpha subunit is a disease driver in 30–40% of cortisol-producing adenoma (CPA) and was associated with reduced DNA methylation at the CYP11B1 promoter that may result in CYP11B1 transcription and hypercortisolemia (Kometani et al. 2017). A second study characterized expression of the protein kinase A subunits in normal adrenal glands and ACA (Weigand et al. 2017). The molecular etiology behind a rare subtype of Cushing syndrome caused by ectopic expression of glucose-dependent insulino tropic polypeptide receptor (GIPR) was unveiled; microduplications at chromosome 19q13 that contain the GIPR locus (Lecoq et al. 2017).

**Adrenocortical carcinoma**

**Outcome and prognostic factors**

Partial response (PR) has been proposed as a surrogate for overall survival in ACC. This study found that most patients with metastatic ACC and long survival times had PR within the first 6 months of systemic therapy, and almost all within the first year. The absence of response after that period could be considered as a treatment failure (Vezzosi et al. 2018). Eighty-two patients with high-risk pediatric ACC were evaluated for outcome and prognostic factors; distant metastases and large tumor volume were associated with unfavorable prognosis (Cecchetto et al. 2017).

**Improved classification and prognosis**

It is clear that the most optimal clinicopathological classification of ACC has yet to be determined. The United States ACC Study Group analyzed 149 patients and proposed a refined TNM classification with a novel T-Stage (Poorman et al. 2018). In a second study, the Helsinki Score, a diagnostic and prognostic system based on the combined evaluation of mitoses and necrosis as well as Ki-67 index, was investigated in 225 cases of...
ACC (Duregon et al. 2017). The third study found that low mitotic tumor grade, Weiss score, global loss of DAXX expression and high phospho-mTOR expression correlated with disease-free survival (Mete et al. 2018).

**Clinical studies**

**Prospective clinical trial**

A Phase 1 study of ARQ 087, an oral pan-FGFR inhibitor, was investigated in patients with advanced solid tumors (Papadopoulos et al. 2017). This was a basket trial that included one patient with a FGFR1-amplified ACC that showed stabled disease upon treatment.

**Retrospective studies, surgical treatment**

Outcome after resection of ACC liver metastases was studied in 77 patients without extrahepatic disease (Baur et al. 2017). The median overall survival was 76.1 months in 43 patients that underwent metastasectomy, compared to 10.1 months in the 34 patients without surgical resection. However, the median disease-free survival in resected ACC was only 9.1 months. A second study investigated perioperative blood transfusion that has been associated with decreased survival in pancreatic, gastric and liver cancer. Perioperative transfusion was associated with earlier recurrence and decreased survival after curative-intent resection of ACC (Poorman et al. 2017). Another study proposed a threshold for surgeon volume to minimize complications and decrease cost associated with adrenalectomy (Anderson et al. 2018). A total of 3496 surgeons performed adrenalectomies on 6712 patients; median annual surgeon volume was 1 case. After adjustment, the likelihood of experiencing a complication decreased with increasing annual surgeon volume up to 5.6 cases (95% CI, 3.27–5.96). Recommendations for the perioperative surgical care of patients with ACC from the European Society of Endocrine Surgeons and ENSAT are now available (Gaujoux & Mihai 2017).

**Oncological treatment**

One hundred forty-five ACC received gemcitabine based chemotherapy, PR or stable disease was achieved in 4.9 and 25.0%, respectively (Henning et al. 2017). No predictive factors could be identified. Claps et al. reported that the combination of metyrapone with mitotane, etoposide, doxorubicin and cisplatin (EDP-M) achieved rapid control of Cushing syndrome induced by cortisol-secreting ACC in three patients (Claps et al. 2017). ERCC1, involved in DNA excision repair, was investigated as a predictive biomarker of platinum-based chemotherapy in 146 ACC but demonstrated negative results (Laufs et al. 2018). A second predictive marker topoisomerase II alpha, showed a positive correlation to EDP-M, disease response or stabilization was observed in 21/30 topoisomerase II alpha positive ACC compared to 5/22 in those without the biomarker (Roca et al. 2017).

**Translating molecular findings to the clinic**

Comprehensive characterization of ACC biology was previously achieved by TCGA and ENSAT consortiums that together proposed a robust molecular classification (Assie et al. 2014, Zheng et al. 2016). Prognostic impacts of these subgroups were analyzed using methodologies compatible with clinical diagnostic use. Jouinot et al. investigated DNA methylation and Sbiera et al. investigated VAV2 gene expression (Jouinot et al. 2017, Sbiera et al. 2017). Both methods revealed a strong correlation to survival that was independent to traditional measures in their multivariate analyses. These studies will pave the way of including new prognostic biomarkers into the traditional classification of ACC.

A study of 60 pediatric ACCs investigated the impact of germline TP53 mutations and showed similar prognosis and outcome regardless of mutation status. Ki67 index was a promising prognostic biomarker also in pediatric ACC (Pinto et al. 2017).

**Liquid biopsy**

Independent studies show that circulating tumor DNA can be found in a subset of ACC with high tumor burden (Creemers et al. 2017, Garnet et al. 2018). These early data implies that liquid biopsy has the potential to be used to estimate relative changes in tumor volume as well as to determine the genetic composition of a subset of ACC. Traces of extracellular vesicle-associated microRNAs in the blood was also found to be useful but for a different purpose; perioperative diagnosis of ACC (Perge et al. 2017).

**Translational research and basic science**

**New genetic risk factors**

Five out of 21 patients with MUTYH-associated polyposis had adrenal lesions; two were hyperfunctioning. Among four patients that underwent adrenalectomy, three had benign tumors and one was oncocytic of uncertain malignant potential (Kallenberg et al. 2017). Traces of...
MUTYH deficiency can be found in tumor mutatomes through a unique signature of DNA mutations. Pilati et al. were able to detect this MUTYH deficiency signature in ACC (Pilati et al. 2017). Finally, succinate dehydrogenase gene mutations were found in four unrelated patients with cortisol-secreting ACC (Else et al. 2017). A majority lacked molecular hallmarks associated to SDHx deficiency.

**ACC pathogenesis**

The TCGA dataset has now allowed researchers not involved in the adrenal field to characterize ACC and compare it to other cancers. Three different studies compared the mutational landscape (Cancer Genome Atlas Network 2017), patterns of selection (disease evolution) (Martincorena et al. 2017) as well as telomere length and somatic alterations (Barthel et al. 2017).

**New treatment candidates and tumor models**

**CDK4-6 inhibitors**

CDK4 and CDK6 inhibitors were suggested to be candidate drugs for treatments of ACC (Hadjadj et al. 2017) and a second study identified palbociclib to inhibit proliferation of human adrenocortical tumor cells (Fiorentini et al. 2018).

**Aurora kinase inhibitors**

The aurora kinase inhibitor AMG 900 increased apoptosis and chemosensitivity to anticancer drugs in the NCI-ACC cell line (Borges et al. 2017).

**Guanine nucleotide exchange factor VAV2**

VAV2 was mentioned earlier as a prognostic factor, this study revealed molecular mechanisms involved and suggest that blocking VAV2 may be a new therapeutic approach to inhibit metastatic progression (Ruggiero et al. 2017).

**Rotterin**

Rotterin was introduced as a novel chemotherapy agent (Zhu et al. 2017) and synthetic high-density lipoprotein nanodisks for targeted delivery to ACC (Kuai et al. 2017).

**mTOR and SSTR2 pathways**

Analyses of the mTOR and SSTR2 pathways in ACC cell lines H295R and SW13 (Germano et al. 2017) revealed that everolimus monotherapy and combinations with either mitotane or pasireotide resulted in growth inhibition.

**Acyl-CoA acyltransferase 1 inhibition**

ATR-101 was found to inhibit cholesterol efflux and cortisol secretion by ATP-binding cassette transporters, causing cytotoxic cholesterol accumulation in ACC (Burns & Kerppola 2017). This compound is of high interest in the treatment of adrenocortical tumors including ACC.

**Tumor models**

A mouse xenograft model of metastatic ACC (Morin et al. 2017) and a transgenic mouse model of metastatic ACC through P53/Rb inhibition (Batisse-Lignier et al. 2017) were described.

**Conclusions**

Clinical and basic research on adrenal tumors is an active field that generated very promising advances during 2017. Prominent examples include an improved understanding of adrenal tumor molecular pathogenesis as well as the introduction of new classifications, molecular markers and tracers for functional imaging. We also highlight international collaboration as a key factor that is likely to accelerate improvements in treatment and outcome of patients with these tumors.

**Declaration of interest**

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