Abdominal Radiology (2020) 45:945–963
https://doi.org/10.1007/s00261-019-02371-y

REVIEW

Adrenal cortical carcinoma: pathology, genomics, prognosis, imaging features, and mimics with impact on management

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Published online: 1 January 2020

Abstract
Adrenocortical carcinoma (ACC) is a rare tumor with a poor prognosis. Most tumors are either metastatic or locally invasive at the time of diagnosis. Differentiation between ACC and other adrenal masses depends on clinical, biochemical, and imaging factors. This review will discuss the genetics, pathological, and imaging feature of ACC.

Keywords Adrenal cortical carcinoma · Adrenal tumors · Ki67 · Weiss score · CT adrenal protocol · MRI · Cushing syndrome

Introduction

Adrenocortical carcinoma (ACC) is a rare malignant tumor arising from the adrenal cortex (1). Approximately 60% of ACCs are functional, producing hormones with a wide range of clinical syndromes depending upon the hormones produced [2]. Many ACCs are incidentally discovered during imaging studies obtained for other reasons [3]. ACCs can occasionally be linked to other endocrine malignances and familial cancer syndromes [4]. Patients with suspected ACC should thus undergo a complete adrenal biochemical panel as well as radiological evaluation [5].

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used imaging modalities for the initial evaluation of adrenal masses. The use of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can help in tumor staging, detection of recurrence, and differentiation of malignant from benign lesions on initial imaging. The initial accurate characterization of ACC based on imaging features and differentiating it from other entities is critical for guiding appropriate management [6].

Epidemiology

ACC is a rare, highly malignant tumor with a reported annual incidence of 1 cases per million in the united states according to the Surveillance, Epidemiology, and End Results-18 registry (SEER) database for ACC cases identified from 1974 to 2014. [7]. The previous reported annual incidence was 0.5–2 cases per million [8]. Females are affected more commonly than males. The reported female-to-male ratio is 1.34:1, and most cases are unilateral. A bimodal age distribution has been described for ACC with one peak occurring in the first decade and a second peak later in the fifth decade of life. However, this bimodal presentation has been questioned with a recent study suggesting a predominantly unimodal distribution with a median age of diagnosis of 55 years [7].

Generally, the diagnosis of ACC is made in one of three scenarios. The majority of patients (40–60%) present with

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signs of excess hormonal synthesis. About one-third present with abdominal pain and other local compressive symptoms related to tumor growth and invasion of surrounding structures [9]. A rising number of cases are discovered incidentally (10–15%), but the probability that an incidentally discovered adrenal lesion is ACC remains relatively low [10]. The most common clinical presentation for functioning ACC is Cushing's syndrome, characterized by symptoms related to excess corticosteroid synthesis including truncal obesity, diabetes, hypertension, easy bruising, and menstrual cycle irregularities [11–13]. In females, virilization resulting from excess androgens may accompany signs of excess cortisol. A small percentage of male patients, present with signs of estrogen excess, such as gynecomastia, breast tenderness, decreased libido, and testicular atrophy. Rarely do patients present with signs of isolated hyperaldosteronism such as hypertension and hypokalemia [11]. Systemic symptoms common with other malignancies, such as weight loss, night fever, and anorexia, can also be seen in ACC [14].

Pathological features of ACC

Differentiating ACC from adrenal adenomas based on histological criteria is not always straightforward, especially with needle biopsy specimens. At gross examination ACCs tend to be large, lobulated, and heterogeneous, with areas of hemorrhage and necrosis [6]. The Weiss criteria (Table 1 [15]) are the most commonly applied criteria in diagnosing ACC and differentiating it from adenoma [16]. The scoring system is based on nine pathological criteria, each of which is weighted equally (one point) when present on pathological specimens. The criteria are subdivided into three main categories:

1) Related to cell cytological features
2) Related to tumor architecture, and
3) Related to tumor invasion and infiltration.

Table 1 Weiss scoring system

Cytological features	High nuclear grade (3 or 4)
	High Mitotic rate > 5 per 50 high power field
	Atypical mitosis
Tumor architecture	Clear cells ≤ 25%
	Necrosis
	Diffuse architecture (> 1/3 of tumor)
Infiltration	Venous invasion
	Sinusoidal invasion
	Capsular invasion

Note Each criterion is given a score of 1. A score ≥ 3 correlates with malignant behavior

Each category has three criteria. A score ≥ 3 favors ACC, and a score of 0–2 favors adenoma, although lesions scoring 2 may still be considered suspicious. [5]. A higher Weiss score correlates with more aggressive tumor behavior [15]. In addition to conventional ACC, there are other rare histopathological subtypes including oncocytic, myxoid, and sarcomatoid variants. Oncocytic ACC is composed of oncocytic cells, with a much lower prevalence of the genetic alterations and mutations detected in comparison with the conventional and myxoid subtype. Only a few cases of myxoid subtype are reported in the literature. The clinical presentation of myxoid variant is comparable to the conventional ACC, and these tumors are usually hormonally active. The last subtype is sarcomatoid ACC which is characterized by more aggressive behavior than the conventional subtype. Differentiating the subtype of ACC at histology can be very challenging [17, 18].

Genomics of ACC

Although the majority of ACCs develop sporadically, many cases arise in association with various familial cancer syndromes [Table 2 [19–23]] including Li–Fraumeni (Fig. 1), Beckwith–Wiedemann, and Lynch syndromes. Several genetic alterations have been noted to play an important role in the pathogenesis of ACC [24]. Most of the drivers for the pathogenesis of ACC are related to mutations or downregulation of tumor suppressor genes, overexpression of certain growth factors, chromosomal aberrations, and dysregulation of certain important signaling pathways [25].

Tumor protein 53 (*TP53*) mutation and insulin growth factor II (IGF-II) overexpression are the most important genetic alterations in the pathogenesis of familial ACC. *TP53* is a tumor suppressor gene responsible for controlling cellular proliferation. Germline mutations of *TP53* are observed in about 70% of patients with Li–Fraumeni syndrome and 20–30% of sporadic ACC [26]. IGF-II is a gene located on chromosome 11p15 and encodes for fetal growth factor. This gene is maternally imprinted and expressed only by the paternal allele. Genetic alterations in the 11p15 region lead to overexpression of IGF-II. Adrenal tissue has abundant IGF-I and IGF-II receptors, and overexpression of this gene is frequently found in patients with ACC [27].

The Wingless iNTegration (WNT) signaling pathway is one of the most commonly involved pathways in the pathogenesis of ACC. During embryogenesis, this pathway is essential for the cell growth and renewal, but dysregulation of this pathway can lead to oncogenesis in various tissues including the adrenal glands. B-catenin and zinc and ring finger protein 3 (ZNRF3) are important regulators of WNT signaling pathway. 30–80% of patients with ACC have abnormal activation of β-catenin, and 21% of them show abnormality of ZNRF3 [28]. c-MET overexpression is also

Table 2 Overview of the common familial cancer syndromes associated with ACC

Familial cancer syndrome	Mode of inheritance	Genes involved	Clinical presentation	Surveillance for adrenal lesions
LFS	AD	TP53 (tumor suppressor)	Predisposition to multiple cancers, including breast cancer (25–30%), sarcomas (25–30%), brain tumors, leukemia, colorectal and ovarian cancer	In children, abdominal ultrasound every 4 months until the age of 18 No screening recommendations for adults due to the lower risk of ACC in this age group
MEN I	AD	Menin (tumor suppressor)	Parathyroid tumors (95%), pancreatic neuroendocrine tumors (95%) and pituitary tumors (40%). Bilateral adrenal cortical hyperplasia is common, and 1–2% may develop ACC	No specific adrenal screening recommendations For newly detected adrenal lesions: If > 3 cm, surgical resection If < 3 cm, follow-up for 6 months and if stable in size; 2-year interval follow-up is recommended
FAP	AD	APC CTNNB1	Multiple colonic adenomatous polyps, increased risk of colorectal cancer and other malignancies as sarcoma, melanoma and ACC	No evidence-based screening recommendations Suggestions of screening abdominal MRI at adolescence or referral for endocrinologist in selected cases with family history of extracolonic involvement
LS	AD	MSH2 MSH6 MLH1 PMS2	Increased risks of colorectal, ovarian, endometrial, and lung cancers. In addition to melanoma, sarcoma and ACC	No guidelines for ACC surveillance in LS given the rarity of the condition
BWS	AD	IGF2 CDKN1C KCNQ10 T1 H19	Abdominal wall defects, macroglossia, hemihypertrophy, and exophthalmos. Increased risk of some cancers such as hepatoblastoma, nephroblastoma, and ACC	No specific guidelines for ACC screening, yet screening of these patients for Wilms tumor and hepatoblastoma allows visualization of adrenal area

ACC adrenocortical carcinoma, *AD* autosomal dominant, *APC* adenomatous polyposis coli, *BWS* Beckwith–Weidman syndrome, *CDKN1C* cyclin-dependent kinase inhibitor 1C, *CTNB1* catenin beta 1, *FAP* familial adenomatous polyposis, *IGF2 i*nsulin growth factor 2 gene, *KCNQ10T1* potassium channel, voltage gated KQT-like subfamily Q, member 1, *LFS* Li–Fraumeni syndrome, *LS* lynch syndrome, *MEN1* multiple endocrine neoplasia, *MSH1-6* MutS protein homolog 2–6, *PMS2 p*ost-meiotic segregation increased 2, *TP53* tumor protein 53

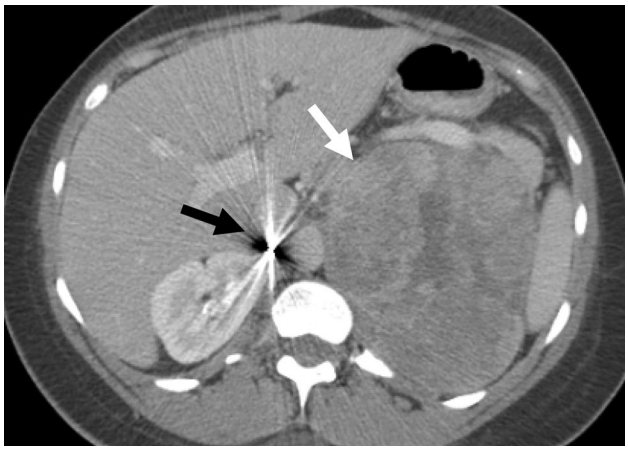

Fig. 1 A 32-year-old female patient with left ACC in the context of Li–Fraumeni syndrome. Axial contrast-enhanced abdominal CT shows a large left suprarenal mass (white arrow). Postsurgical changes of a previous right ACC resection are noted (black arrow)

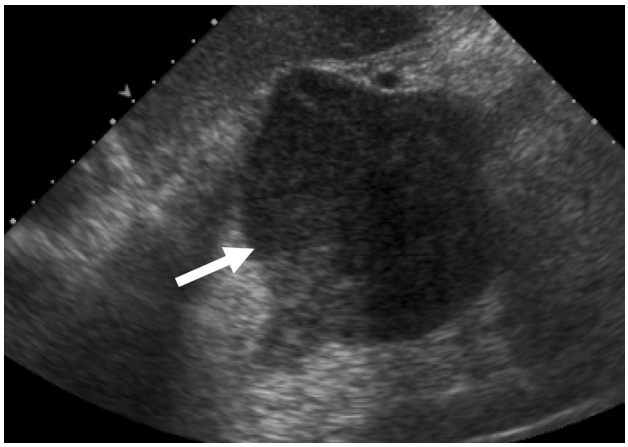

Fig. 2 A 69-year-old female patient evaluated for left upper quadrant pain. Abdominal ultrasonography shows a 7 cm solid hypoechoic suprarenal mass (white arrow) that proved to be ACC

an important molecular change in ACC that is believed to occur as a resistance mechanism to radiation therapy and chemotherapy [29].

A number of chromosomal aberrations have been detected in ACC using comparative genomic hybridization (CGH). The most commonly detected aberrations are losses on chromosomes 1, 17, 22, 2, and 11, and gains on chromosomes 5, 12, 19, and 4. It is suggested that tumor suppressor genes and oncogenes might be located on the regions of chromosomal loss and gain [25]. ACC is a heterogeneous cancer with multiple molecular and genetic drivers. Despite the recent advances in understanding the molecular and genetic elements contributing to the pathogenesis of ACC, there remain many unexplored areas. More understanding of the correlation between the molecular, clinical, and pathological profile of ACC is still needed [18].

Prognostic indicators in ACC

Clinical, molecular, and pathological features determine the prognosis of patients with ACC. Patient age and initial stage at diagnosis are considered two of the most important predictors of survival, with a poorer prognosis in patients with advanced age or metastatic disease at the time of diagnosis. Furthermore, hormonally functioning tumors have a relatively worse prognosis, which may be related to the effects of Cushing syndrome and immunosuppressive effect of corticosteroids, which can lead to "tumor flaring" [1, 30].

Ki67 is among the most important markers in differentiating benign from malignant adrenal lesions. Lesions with Ki67 index greater than 5% are likely to be malignant. Moreover, Ki67 positivity is considered the single most important predictor for local recurrence after complete R0 surgical resection of ACC. Tumors with less than 10% Ki67 have significantly better clinical outcomes than those with greater than 10% Ki67 [17].

Imaging features of ACC

Imaging provides information about the malignant potential of adrenal masses, especially for localized lesions without extra-adrenal metastases. Unfortunately, even with these tools, the definitive characterization of adrenal masses remains challenging [12]. The presence of distant metastases is a reliable sign of malignancy. Other radiological features suspicious for malignancy include large tumor size and heterogeneous attenuation/signal intensity and enhancement pattern; the latter two may reflect the presence of necrosis, intra-tumoral hemorrhage, and calcification [6].

Ultrasonography

Some have reported high sensitivity for detecting adrenal masses ([31] (97% for masses >20 mm and 94% for masses < 20 mm) [32], but further characterization may be limited by body habitus and operator skill [33]. By ultrasound, ACC most commonly appears as a rounded or oval well-defined hypoechoic mass (Fig. 2), with a minority displaying a thick partial or complete echogenic rim [34].

The echotexture depends on the size of the lesion and the degree of internal hemorrhage and necrosis. Small lesions are often homogeneous but demonstrate increased heterogeneity with increasing size. Calcifications within the lesion appear as echogenic foci with posterior acoustic shadowing [35]. Color Doppler may demonstrate hypervascularity, due

to possible neovascularity [36]. Displacement of adjacent organs by larger masses can also be identified by ultrasound [33].

Computed tomography (CT)

ACCs are typically large, with roughly 70% of tumors larger than 6 cm at the time of diagnosis [6]. Size of the adrenal tumor, pattern of contrast enhancement, and degree of heterogeneity by CT are all important predictors of the malignant potential of the adrenal lesion [37]. ACC is typically heterogeneous by CT and displays mixed intra-tumoral attenuation (Fig. 3). An attenuation value of more than 10 HU on non-contrast CT has high sensitivity for detecting malignancy (93%), but a specificity of only 71–73% [38]. Contrast enhancement is heterogeneous and may be increased peripherally due to central necrosis. ACC characteristically displays less washout of contrast than benign adrenal adenomas (absolute washout < 60% and relative washout < 40%) (Fig. 4) [39]. However, the use of adrenal washout characteristics should be reserved for homogenous well-defined masses. The size of the lesion and the heterogeneity trump washout properties, which depend on the sampled region of the mass [40]. Punctate, patchy, or nodular calcifications are found in 30% of ACC [39, 41].

An irregular tumor margin is a sign of aggressiveness; however, its absence is not a reliable sign of benignity. A thin rim of well-defined enhancement commonly detected around ACC likely represents the tumor capsule [42].

Invasion of periadrenal fat and the surrounding organs or vasculature are other specific features of malignancy (Fig. 5) [6, 42]. IVC invasion is common at the time of diagnosis, and therefore, it is recommended that CT images extend to the level of the right atrium to exclude right atrial thrombus [41]. Metastases are also relatively common at time of presentation (Fig. 6), and the most common sites are in the liver, lung, bone, and retroperitoneal lymph nodes [43].

Fig. 3 Axial contrast-enhanced abdominal CT, showing the typical imaging features of ACC in a 50-year-old female patient. A large heterogeneously enhancing solid left adrenal mass with peripheral heterogeneous enhancement (black arrow) and a central hypodensity compatible with necrosis (white arrow) is noted

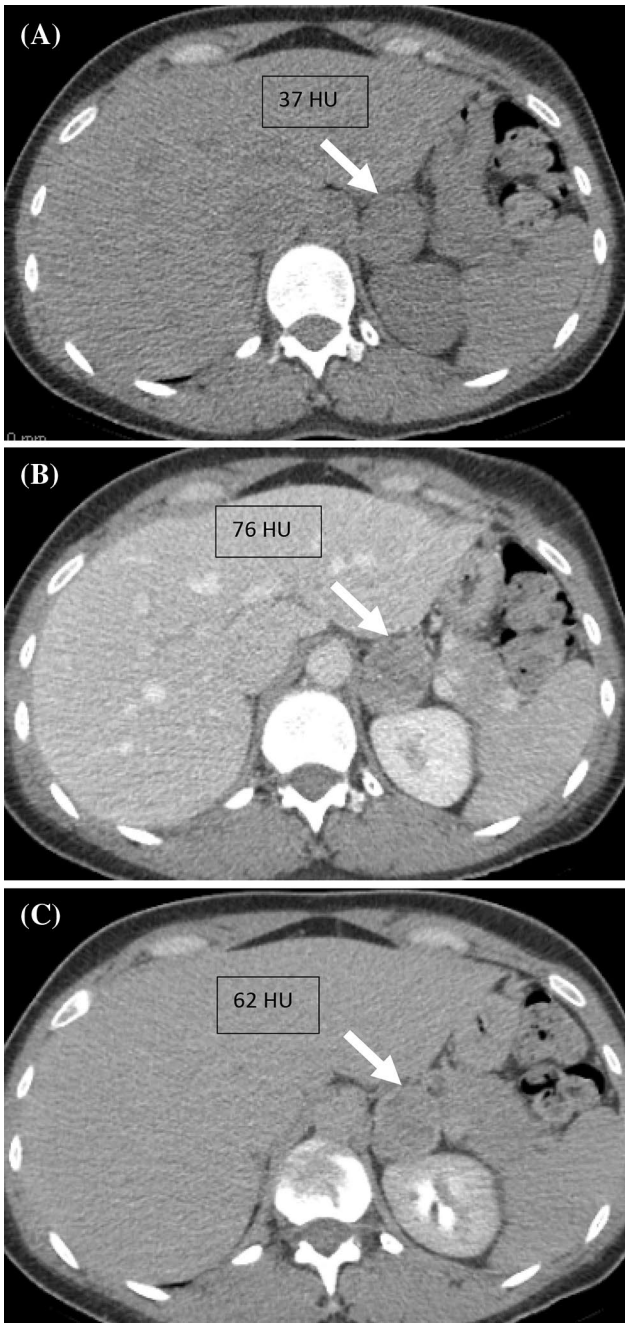

Fig. 4 A 53-year-old female with incidentally discovered left adrenal mass (white arrows). Axial non-contrast (**a**), venous (**b**), and delayed (**c**) post-contrast CT images show a left adrenal mass with attenuation values of 37 HU, 76 HU, and 62 HU in the non-contrast, venous, and delayed images, respectively. The absolute washout for this lesion is 35.9%, and the relative washout is 18.4%. The washout was not consistent with adenoma. This mass was pathologically proven ACC

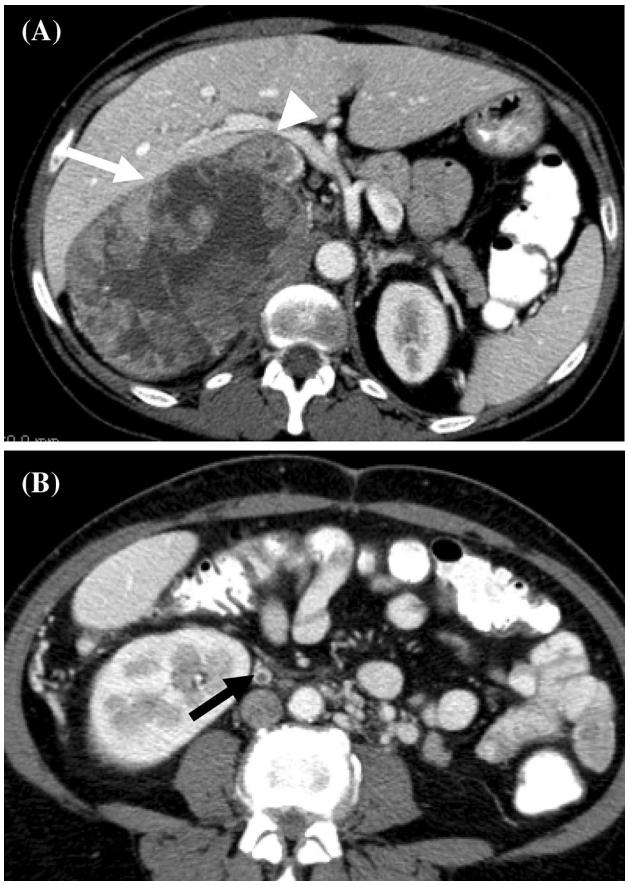

Fig. 5 A 59-year-old woman with ACC. Axial contrast-enhanced abdominal CT (**a** and **b**) shows large heterogeneously enhancing right suprarenal mass (white arrow) with enhancing tumor thrombus extending into the Inferior vena cava (white arrowhead) and luminal defect within the right gonadal vein indicating thrombosis (black arrow)

Magnetic resonance imaging (MRI)

ACC displays heterogeneous signal intensity on both T1 and T2 WI due to areas of hemorrhage and necrosis. Areas of intrinsic T1—shortening, most commonly indicates the presence of hemorrhage (Fig. 7). Necrosis appears as areas of T2—prolongation [6]. Rarely, ACC may demonstrate intracellular lipid, which can be appreciated on chemical shift imaging, losing signal on out-of-phase imaging [39]. Generally, the area of signal loss is small (< 30% of lesion), in contrast to lipid-rich adenomas which more commonly demonstrate a more uniform drop in signal (Fig. 8) [6]. Other suspicious findings such as heterogeneity of the lesion and large tumor size should aid in avoiding diagnostic error when ACCs contain intracellular fat [44]. MRI has better soft tissue resolution than CT giving it the added value of detecting venous invasion by tumor, differentiating bland from tumor thrombus, and identifying the upper limit of tumor thrombus extension [14, 45–47].

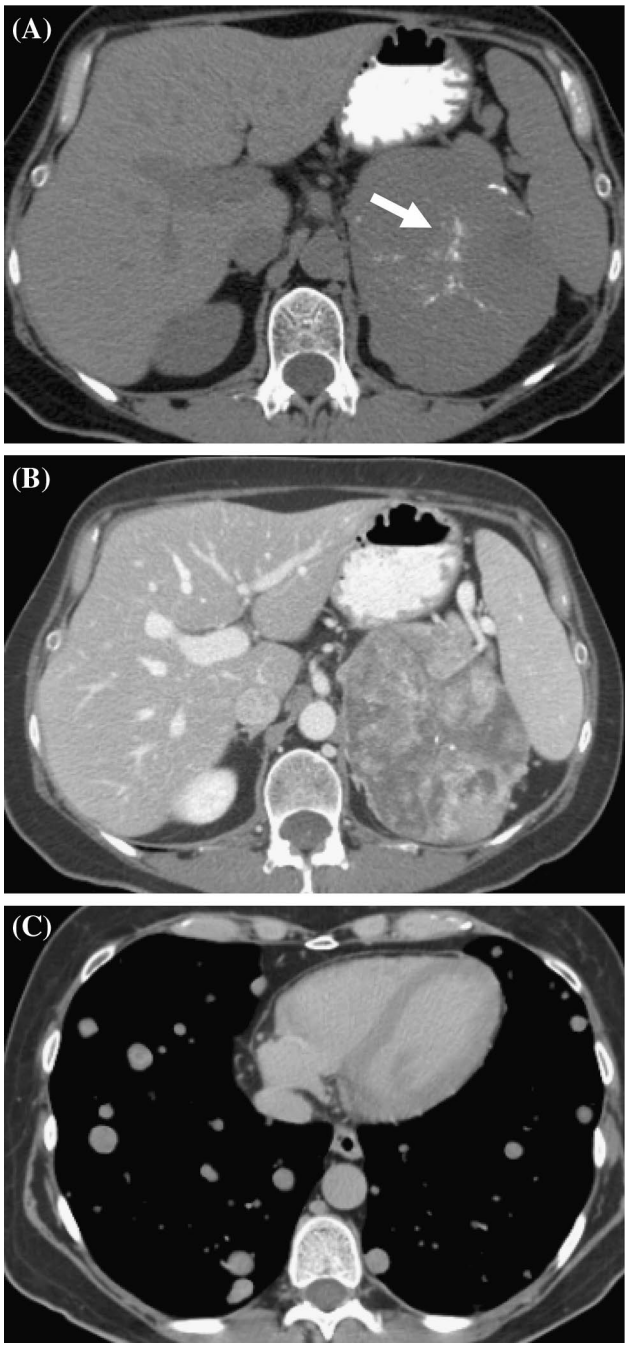

Fig. 6 A 40-year-old male patient with metastatic ACC. **a** Axial unenhanced CT of the abdomen shows a hypodense left adrenal mass with scattered calcifications (white arrow). **b** Axial contrast-enhanced CT of abdomen shows heterogeneous enhancement of the left large adrenal mass. **c** Axial CT chest shows multiple bilateral metastatic pulmonary nodules

A study evaluating treatment outcomes of children with ACC reported that MRI is superior to both ultrasonography and CT in the detection of intravascular invasion with sensitivity of 100 %, compared to 50% by ultrasound and 66% by CT [48].

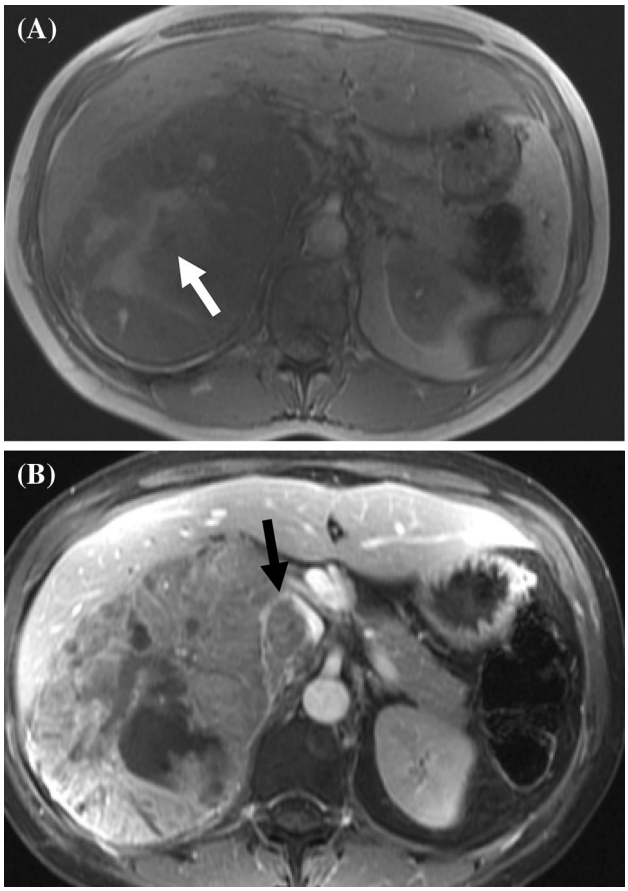

Fig. 7 A 31-year-old with ACC. **a** Axial T1-weighted MR image shows a large right suprarenal mass with hemorrhagic component (white arrow). **b** Axial T1 post-contrast MR image shows the large heterogeneously enhancing right adrenal mass invading the inferior vena cava (black arrow)

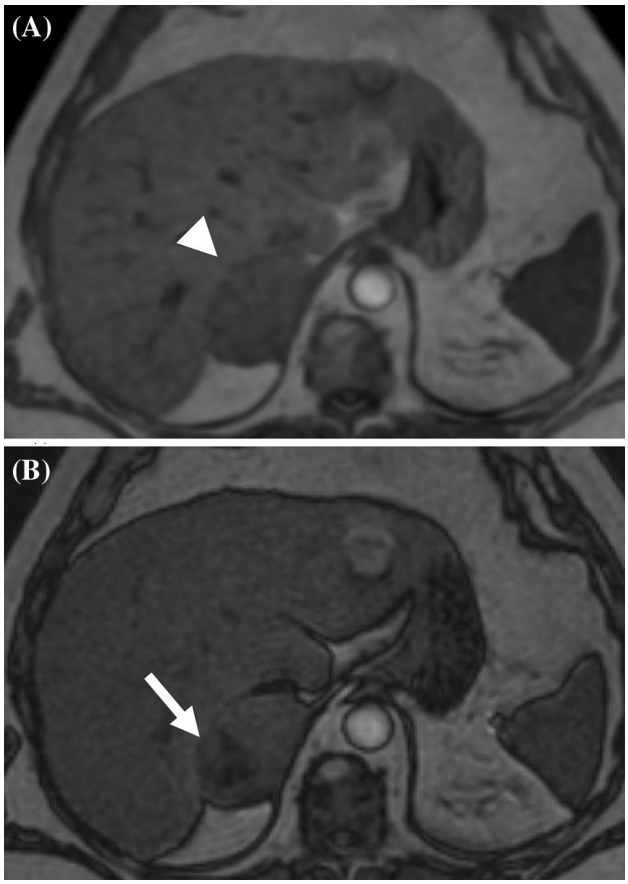

Fig. 8 A 46-year-old male patient presenting with hypertension and weight gain. **a** Axial in-phase MR image shows a hypointense right adrenal mass (white arrowhead). **b** Axial out-of-phase MR image exhibits non-uniform loss of signal in the adrenal mass (white arrow). Pathology of the mass revealed ACC

Diffusion-weighted imaging (DWI) is not of significant value in characterization of adrenal lesions due to the overlapping apparent diffusion coefficient (ADC) values between benign and malignant adrenal masses [49].

Magnetic resonance spectroscopy (MRS) has been recently implemented in oncological practice for the characterization and post-treatment evaluation of various tumors [50]. The utility of MRS in the characterization of adrenal lesions is limited by the deep anatomical location of adrenal gland, its proximity to other organs with marked susceptibility artifact, and the heterogeneous nature of lesions [51]. Analysis of the metabolic profiles of various adrenal masses using MRS has shown that the metabolic fingerprint of ACC is distinct from adrenal adenoma, reflecting its malignant properties. Choline-containing compounds were higher in ACC due to the high cellular turnover. Anaerobic metabolism markers such as lactate were more abundant in ACC. Acetate, which is a major contributor of fatty acid synthesis through the beta oxidation pathway, is remarkably elevated in ACC, explained by the high fatty acid content of ACC. The combination of significantly relative higher levels of choline, acetate, and lactate in ACC can aid in differentiating ACC from adenomas [52]. Another MRS study categorized adrenal lesions into four groups including adenoma, ACC, pheochromocytoma, and metastases. Distinguishing adenomas and pheochromocytomas from ACC and metastases using the choline–creatinine ratio, choline–lipid ratio, and lipid–creatinine ratio was possible with substantial sensitivity and specificity. Also, a 4–4.3 ppm/creatinine ratio greater than 1.5 enabled the differentiation of pheochromocytomas and ACC from adenoma and metastasis with 87% sensitivity and 98% specificity [53].

Functional imaging

Fluorodeoxyglucose positron emission tomography (FDG-PET) has the potential to differentiate benign and malignant adrenal lesions by virtue of their metabolic activity. The

adrenal uptake is compared to the background activity in the liver either visually or quantitatively by measuring the standardized uptake value (SUV) within the region of interest. Normal adrenal glands have FDG uptake equal to or less than the liver. Multiple studies have demonstrated the utility of FDG-PET in the discrimination of benign and malignant adrenal masses to varying degrees [54–57]. The reported sensitivity and specificity of FDG-PET in the previous studies ranged between 92 and 100% and 80 and 100%, respectively. A recent meta-analysis reported a sensitivity and specificity of 91% for FDG-PET in discriminating benign from malignant adrenal lesions [56]. FDG-PET also showed higher prognostic performance than contrast-enhanced CT (CECT) in diagnosing ACC, with an accuracy of 93.4% for FGD-PET versus 75% for CECT [58]. In general, the negative predictive value and sensitivity of FDG-PET in characterization of adrenal masses are much higher than the positive predictive value and specificity [10]. Currently, the American College of Radiology committee on incidental findings suggest utilizing FDG-PET in patients with a prior cancer history and indeterminate adrenal masses or indeterminate adrenal masses which are less than 4 cm [59].

FDG-PET is a complementary imaging tool to CT and MRI for the initial staging of ACC and detection of distant metastases [60]. FDG-PET was found to be more useful in the detection of ACC recurrence in the operative bed compared to routine anatomical imaging (Fig. 9), yet it was less sensitive in the detection of lung and liver metastasis [61]. The degree of FDG uptake by the tumor does not correlate with the overall or disease-free survival, and it cannot be used as an independent prognostic predictor as in other malignancies like lymphoma and lung cancer [62]. Nevertheless, in a more recent series of 106 ACC patients with metastatic disease, FDG-PET slightly outperformed conventional cross sectional imaging with respect to monitoring response to chemotherapy [63]. Despite the ability of FDG-PET to differentiate benign from malignant adrenal lesions, difficulty remains in discriminating primary adrenal malignancy from metastasis. ^{11}C-metomidate has a high affinity for key enzymes involved in steroidogenesis. Therefore, ^{11}C-metomidate accumulates only in adrenal cortical origin tissues, such as adenomas and ACC, and thus may differentiate these entities from pheochromocytoma or adrenal metastases [64, 65].

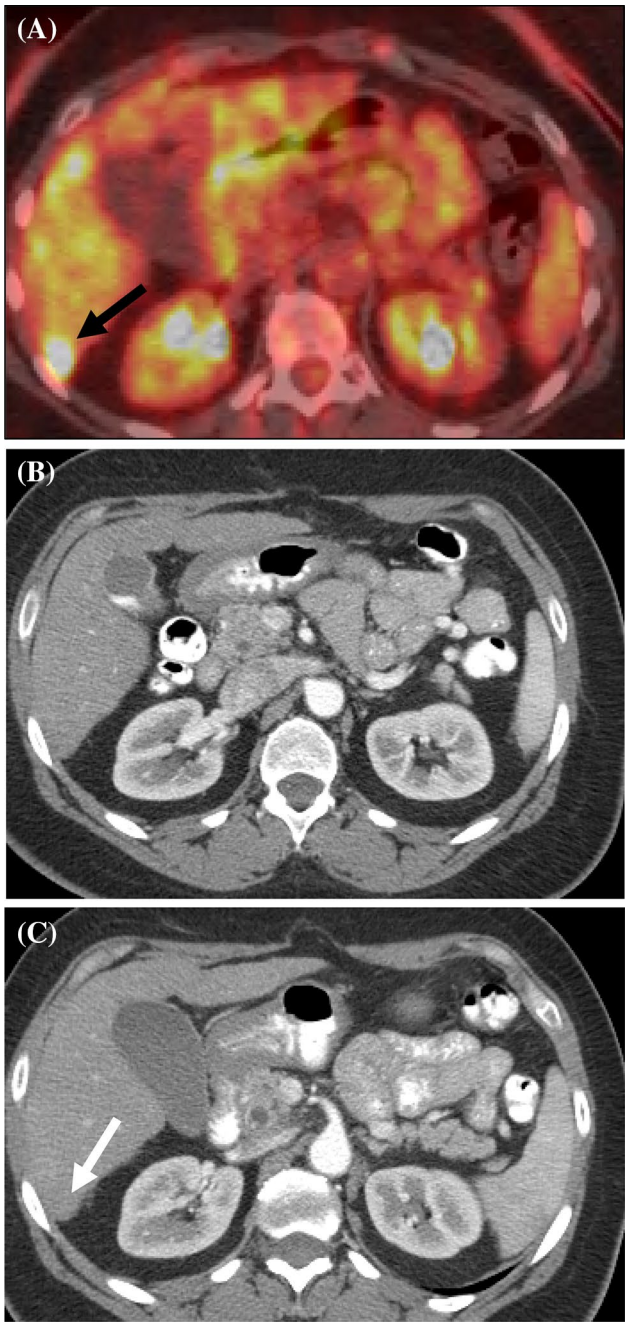

Fig. 9 A 40-year-old male patient with previous history of right ACC resection. **a** PET CT shows a focus of avid FDG uptake (black arrow) in the liver. **b** Axial image from a concurrent contrast-enhanced abdominal CT **b** did not reveal any abnormality corresponding to the area of the avid FDG uptake. **c** Follow-up CT 3 months later; the area of abnormality detected in the previous PET CT is more appreciated by CT scan (white arrow)

Radiomics and texture analysis

Radiomics is a developing field of medical imaging which involves the extraction of quantitative data from routine CT and MRI studies, converting the visual information in the routine medical images into minable data. This can be further analyzed to help in decision making, especially in the field of medical oncology [66]. Radiomics has multiple potential application including distinguishing benign from malignant lesions, prediction of treatment outcomes, assessment of treatment response, and prediction of cancer genetics and histopathological subtypes [67]. The utilization of second-order radiomic features extracted from unenhanced

MRI images may be useful for the classification of adrenal lesions into lipid-rich adenoma, lipid-poor adenoma, or non-adenomatous lesion. In one study, texture analysis performed via a machine learning algorithm demonstrated superior diagnostic accuracy compared to an experienced radiologist in distinguishing these lesions, though the difference was not statistically significant [68]. Radiomic features derived from contrast-enhanced CT have shown statistically significant differences between malignant adrenal nodules and lipid-poor adenomas, though the diagnostic accuracy was lower than that obtained with unenhanced CT attenuation values or chemical shift imaging on MRI [69]. A recent study assessing quantitative CT texture analysis of 54 histopathologically proven adrenal masses looked at ACC and adenomas which were assessed by two blinded radiologists based on morphological criteria. Comparison of prediction accuracy and inter-observer agreement showed that the texture predictive model had a higher mean accuracy of 82%, whereas the mean accuracy for the radiologists was less at 68.5% ($p < 0.0001$). The study thus concluded that CT texture analysis can improve differentiation of ACC and adrenal adenomas [70].

Staging of ACC

Accurate staging is a crucial step in treatment planning and in determining the prognosis of ACC [10]. Survival drops precipitously with advanced stages, with 90% 1-year survival for Stage I disease plummeting to 29% 1-year survival for Stage IV disease [71]. A CT scan of the chest is a critical component for accurate staging due to its superiority to other imaging modalities in identification of pulmonary metastases. Abdominal or pelvic CT or MRI covers the majority of other metastatic sites [10], although MRI is superior to CT in the detection of vascular invasion [6, 14, 45]. Unless clinically suspected, focused imaging for bony and brain metastases is not essential as both are uncommon sites of metastases [10]. The European Network for the Study of Adrenal Tumors (ENSAT) system is the most commonly used system to stage ACC [72]. According to ENSAT system, Stage I includes lesions < 5 cm and stage II lesions > 5 cm, both with no evidence of metastatic involvement of adjacent organs, periadrenal fat, or lymph nodes. Stage III includes lesions of any size with evidence of surrounding organs, periadrenal fat, and/or lymph node involvement, but no evidence of distant metastasis. Stage IV is limited only to lesions with evidence of distant metastasis [72]. This system is also adopted in the recently published edition of AJCC staging manual (8th edition). It has been proposed that future staging schemes incorporate lymphovascular invasion, a known poor prognostic indicator, to better predict survival [73].

Approach to atypically presenting ACC

Although ACCs most commonly present with features of excessive hormonal secretion or compressive symptoms due to the enlarging mass, an increasing number of cases are discovered incidentally [14]. Adrenal incidentalomas are adrenal lesions greater than 1 cm, discovered during imaging studies for unrelated reasons [74]. The majority of adrenal incidentalomas are benign. The determination of the malignant potential of an adrenal mass depends on the size of the lesion, imaging features, and hormonal status [75]. Hormonal evaluation is a fundamental step in the assessment of adrenal incidentalomas with the exception of adrenal cysts, myelolipoma, and adrenal hemorrhage [76]. All hormonally functioning lesions should be considered for surgical removal. Currently, the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons recommend biochemical assessment of all incidentally discovered adrenal lesions [59]. Incidentally discovered lesions greater than 4 cm are suspicious for primary or metastatic malignancy and patients should have biochemical assessment and a thorough history elicited to exclude a previous malignancy. Lesions >4 cm with benign radiological features could be considered for surgery or follow-up if the patient is not a good surgical candidate [59, 76]. With respect to an indeterminate mass, size > 4 cm is a sensitive but nonspecific indicator of malignant potential of an adrenal lesion. In general, these patients are considered for surgery, taking into account age and comorbidities [76]. Lesions ranging between 1 and 4 cm should have further assessment for signs of benignity. Adrenal lesions with benign features such as pre-contrast attenuation <10 HU, loss of signal on out-of-phase images compatible with intracellular lipid, and macroscopic fat do not require further imaging. Lesions with pre-contrast attenuation > 10 HU should have imaging with a dedicated adrenal protocol to quantify the degree of contrast washout. Typically, adenomas show absolute washout > 60% and relative washout > 40%, with high sensitivity and specificity in differentiating adenomas from non-adenomas [59]. MRI is an alternative for further characterization of indeterminate adrenal lesions due to its ability to detect intracellular lipid. There is no specific recommendation for the best imaging modality to be used. MRI is generally more expensive and time-consuming than CT, but has the advantage of not using intravenous contrast and lack of ionizing radiation [75].

FDG-PET/CT may be an important ancillary study in indeterminate lesions, especially in patients with known extra-adrenal malignancy or inpatients with indeterminate lesions measuring < 4 cm. Indeterminate adrenal lesions are small percentage of adrenal lesions that do not show imaging features diagnostic of benignity by CT and MRI. Indeterminate adrenal lesion by imaging might represent

lipid-poor adenoma, pheochromocytoma, primary or secondary malignancy [59, 77, 78]. Adrenal/liver SUV ratio > 1.8 demonstrates 87% sensitivity and 84% specificity in differentiating benign from malignant lesions [38]. If the lesion is non-functioning and indeterminate by imaging criteria, follow-up imaging using the same modality is recommended. There is no clear agreement regarding the optimum follow-up or surveillance period, ranging from 3 to 6 months for more suspicious lesions to 12 months for more benign-appearing lesions [76]. A more than 20% increase in the size of the lesion or a 5 mm increase in maximum diameter is an indication for surgery. If there is measurable growth that does not meet this threshold, continued follow-up in 6–12 months is recommended [79].

Although the presence of macroscopic fat is most commonly seen in benign myelolipoma, ACC may show areas of macroscopic fat as well (Fig. 10). Other imaging and biochemical features should be kept in consideration to differentiate this rare manifestation of ACC from myelolipoma [80], as previously discussed. With any adrenal lesion, the appropriate workup depends on a variety of factors. Incorporating clinical, imaging, and biochemical data allow the formulation of a proposed systematic approach (Fig. 11).

ACCs may also coexist with other adrenal neoplasms representing the so-called adrenal collision tumors. These are histologically distinct neoplasms coexisting in the same location without histological intermixing. Collision tumors have been described in the adrenal gland including adrenocortical cancer with myelolipoma and ACC with other lesions such as adenoma.

Collision lesions pose a diagnostic dilemma owing to varying enhancement patterns between the two entities which may lead to inaccurate diagnosis. Hemorrhage into an ACC can also mimic a collision lesion, and it is important to differentiate these two pathologies [81].

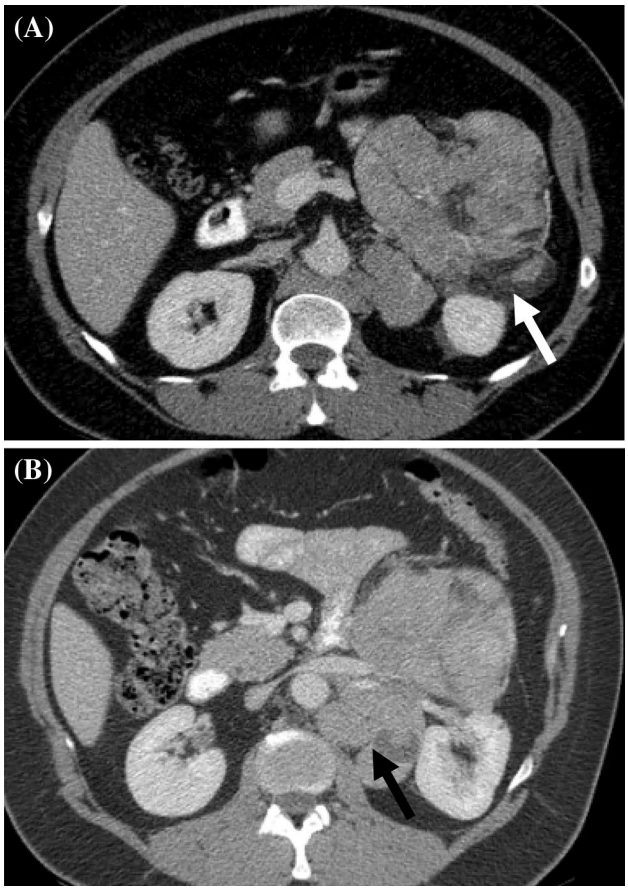

Fig. 10 Axial contrast-enhanced abdominal CT (**a** and **b**) shows a large mass in the left adrenal bed with areas of macroscopic fat (white arrow) and retroperitoneal lymphadenopathy (black arrow). This mass proved to be ACC despite the presence of mature fat component on imaging

Role of image-guided biopsy

Image-guided biopsy is seldom needed in patients with adrenal tumors. Oftentimes, in patients with large adrenal masses, surgical resection is favored over a biopsy, as surgery has therapeutic and diagnostic benefits [10]. There are two types of adrenal biopsies: fine-needle aspiration (FNA) and core biopsy. Both can be used depending on preference of the radiologist performing the procedure. Fine-needle aspiration is preferred in hypervascular masses and lesions that are surrounded by bowel to avoid inadvertent bowel wall injury during the procedure. If an FNA is performed, assessment of the FNA sample for adequacy is recommended, necessitating availability of the pathologist at the time of the procedure. Core biopsy may be performed, especially when larger tissue samples are needed for flow cytometry in the setting of suspected lymphoma [31]. Although biopsy samples by either method have an established diagnostic role in multiple solid tumors as pancreatic and hepatic tumors, the role of biopsy in the diagnosis of ACC is less clear [82].

Multiple studies have reported a high sensitivity (81–100%) and specificity (96.3–100%) for fine-needle aspiration biopsy in adrenal masses. A study on 204 adrenal lesions reported 86% sensitivity and 88% specificity for core-needle biopsy in diagnosing adrenal masses [83]. Routine adrenal biopsy is not recommended in suspected ACC to avoid needle track metastasis [84]. It is often challenging for pathologists to differentiate benign from malignant adrenal cortical masses even if the whole tumor specimen is available. The small sample size from the biopsy may not be sufficient to elaborate all Weiss score criteria which are essential in differentiating adenomas from ACC [85]. Biopsy is generally reserved for select cases, such as for staging in patients with known primary malignancy and in cases when an infiltrative process is suspected such as histoplasmosis or tuberculosis [10, 86]. Biochemical exclusion

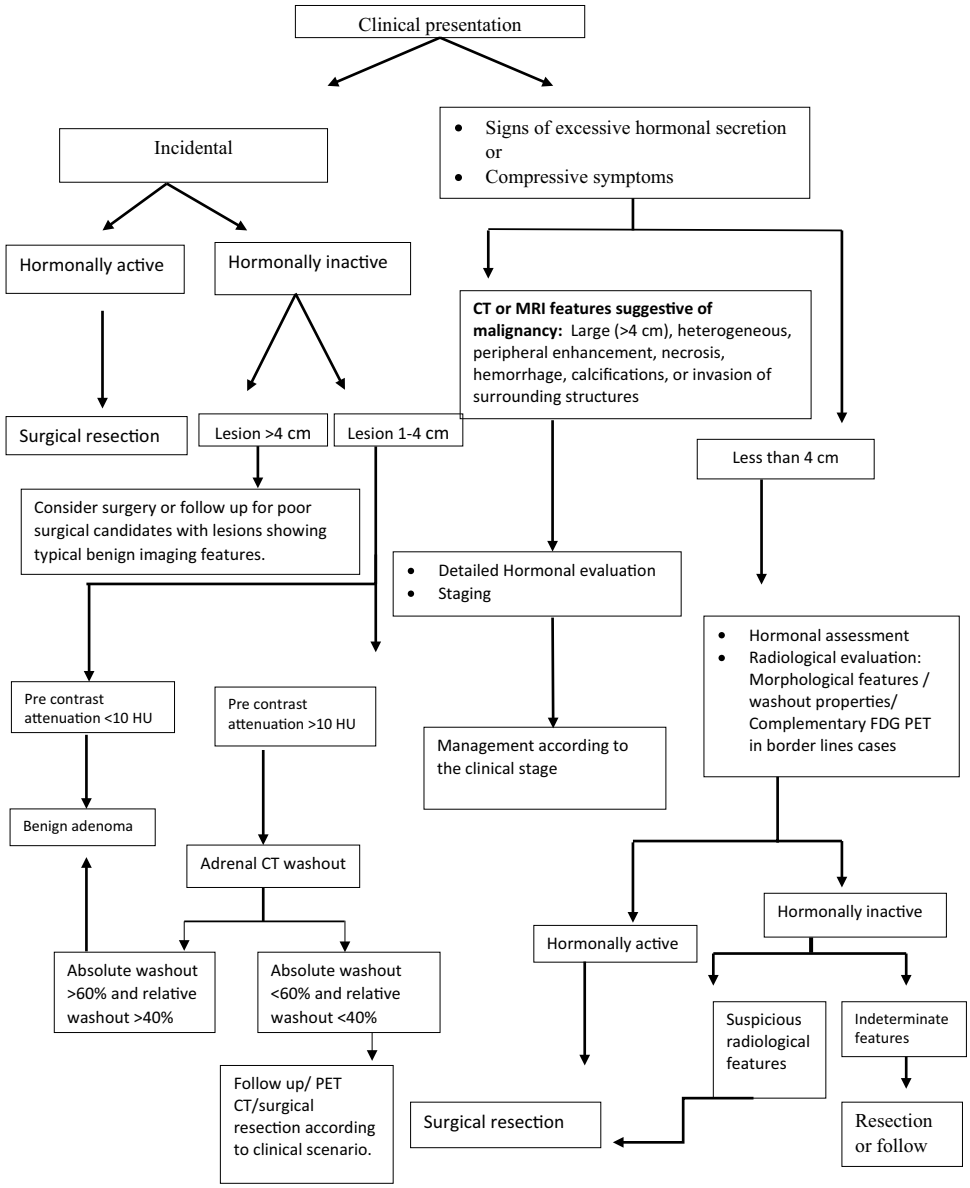

Fig. 11 Algorithm for the evaluation of adrenal lesions

of pheochromocytoma before biopsy is essential to avoid life-threatening hormonal surge during the biopsy procedure [87].

Mimics of adrenocortical carcinoma

Pheochromocytoma

Pheochromocytoma can have a variable imaging appearance, resulting in a diagnostic challenge (Fig. 12). Smaller lesions usually display more uniform homogenous enhancement than larger ones and show calcification in 10% of cases. Almost all pheochromocytomas have high attenuation values (> 10 HU) on pre-contrast CT, though they rarely may have fatty content, resulting in attenuation values less than 10 HU. High attenuation may be attributed to intra-tumoral hemorrhage in some cases [88]. Contrast enhancement and washout properties of pheochromocytoma are variable. Although pheochromocytoma typically shows intense contrast enhancement, the washout properties overlap with both benign and malignant lesions. The classic MRI appearance of pheochromocytomas, i.e., hyperintense T2 signal, sometimes referred to as the "lightbulb sign," is not a sensitive or specific feature of pheochromocytoma [83, 84]. The clinical presentation is variable among patients, with the majority presenting with signs and symptoms of excess catecholamine such as hypertension, diaphoresis, palpitations, anxiety, and headache. Roughly 10% of pheochromocytomas are non-functioning/poorly functioning and therefore asymptomatic [89]. All patients with adrenal masses should be tested for serum or urine metanephrines [90]. Biochemical

Fig. 12 A 64-year-old female patient presenting with hypertensive crisis. Axial contrast-enhanced abdominal CT shows a large lobulated heterogeneous suprarenal mass (white arrow) and left retroperitoneal enhancing mass (white arrowhead). Hormonal assessment revealed elevated metanephrines and malignant pheochromocytoma was suspected. Pathology revealed right adrenal pheochromocytoma, and the left paraaortic enhancing mass was determined to be extra-adrenal paraganglioma

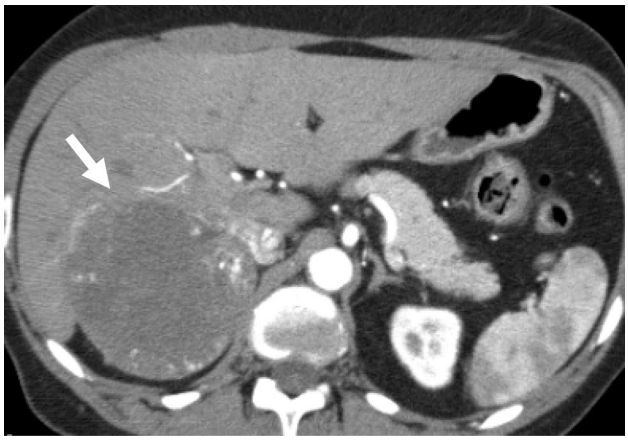

Fig. 13 A 63-year-old female patient with incidentally discovered right large adrenal mass. Axial contrast-enhanced abdominal CT shows a large heterogeneous suprarenal mass with areas of nodular enhancement (white arrow). ACC was the suggested diagnosis radiologically. By pathology the mass lesion proved to be adrenal adenoma

evaluation readily discriminates pheochromocytoma from ACC in most cases, yet non-functioning large lesions still represent a diagnostic challenge [6].

Adrenal adenoma

Adrenal adenoma is the most commonly encountered adrenal mass and is typically homogenous with mild contrast enhancements. Approximately 70% of adenomas are lipid-rich, with pre-contrast attenuation < 10 HU. Lipid-poor adenomas generally have attenuation value ranging between 10 and 30 with a characteristic washout pattern as previously discussed [89]. Greater than 20% drop of signal during out-of-phase imaging is also a diagnosis of adenoma [91]. The average size of adrenal adenomas has been reported to be 2–2.5 cm in size, and typically they do not exceed 3 cm [40]. Larger adenomas tend to be more heterogeneous with possible calcifications [92]. Differentiation of large heterogeneous adenomas from carcinomas is often not possible by imaging (Fig. 13), and lesions larger than 4 cm are generally managed as presumed malignant lesions [6, 93].

Adrenal metastasis

Adrenal metastases (Fig. 14) represent a small portion of incidentally discovered adrenal masses. Bilateral involvement of the adrenals with metastases is more common than unilateral involvement [39]. Isolated adrenal metastases in the absence of other systemic metastases are rare [94]. Metastases should be considered in any patient with a known primary malignancy and bilateral adrenal lesions or when there is evidence of other metastatic sites [6]. The most common primary malignancies that metastasize to the adrenals include breast, colon, lung, and renal cancers as well as melanoma [39].

Metastatic lesions usually have a CT attenuation value >10 HU and demonstrate less contrast washout when compared to adenoma [95]. FDG-PET usually shows high uptake, but this is dependent on the FDG avidity of the primary tumor. Rarely metastatic adrenal lesions may show imaging overlap with adenomas including intracellular lipid and washout on CT [96].

Fig. 14 A 65-year-old male patient with incidentally discovered 7 cm left adrenal mass adrenal mass that was suspicious for ACC as the patient had no known primary. The pathological diagnosis was consistent with metastatic acinar carcinoma. Further work up detected jejunal acinar cell carcinoma

Adrenal lymphoma

Adrenal lymphoma is most commonly secondary in the presence of diffuse disease, and primary adrenal lymphoma is extremely rare. Lymphomatous involvement of the adrenals is detected by autopsy in 25% of patients with advanced lymphoma [94]. About 70% of primary adrenal lymphomas are bilateral [97]. Lymphomas are large soft tissue masses of average size 8 cm, often maintaining the triangular shape of the gland (Fig. 15). Most lesions are hypoattenuating by CT and display mild-to-moderate contrast enhancement. By MRI, they usually show low T1 signal and increased T2 signal as well as diffusion restriction due to its high cellularity. Calcifications are rarely seen unless the patient has been previously treated. The presence of bilateral large adrenal masses in the absence of an extra-adrenal primary malignancy should raise concern for adrenal lymphoma [39]. Elevated serum lactate dehydrogenase is a common finding in aggressive lymphomas and may help in the differentiation of adrenal lymphomas from other large adrenal masses [98].

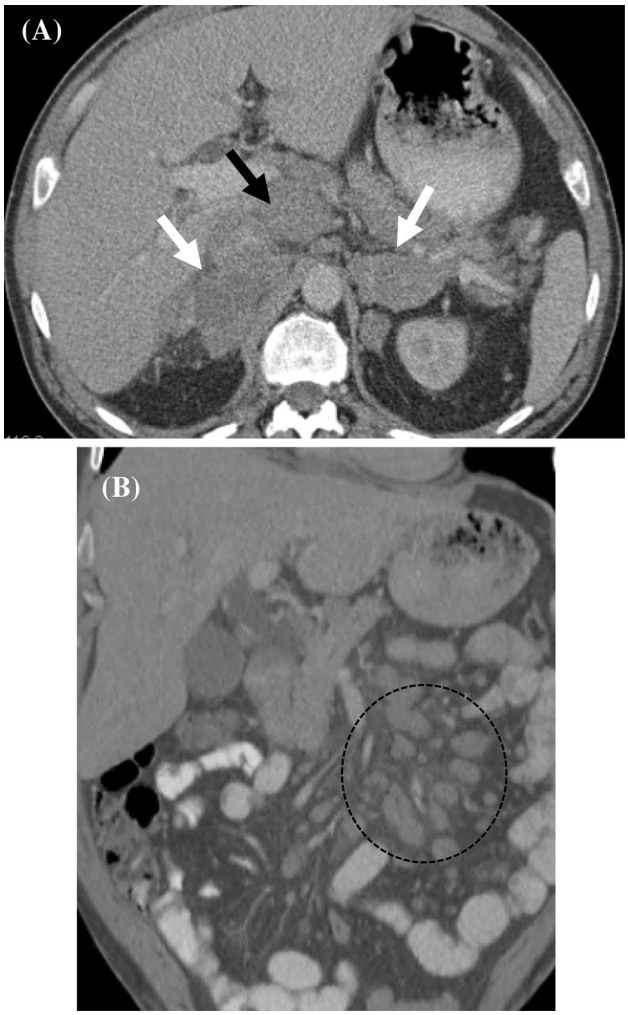

Fig. 15 A 50-year-old male patient with abdominal lymphoma and secondary bilateral adrenal involvement. **a** Axial contrast-enhanced abdominal CT shows bilateral hypoenhancing adrenal masses (white arrows) and enlarged porta hepatis lymph nodes (black arrow). **b** Coronal contrast-enhanced abdominal CT of the same patient shows mesenteric adenopathy (circle)

Ganglioneuroma and ganglioneuroblastoma

Both are uncommon tumors that can arise anywhere along the sympathetic chain and can occasionally arise from the adrenal medulla. Ganglioneuromas are benign tumors that typically display low homogenous CT attenuation and mild contrast enhancement. Calcifications are noted in 42–60% of lesions [99]. Ganglioneuromas exhibit low homogenous T1 signal intensity and heterogeneous high T2 signal intensity, likely attributable to the combination of myxoid components and ganglion cells [100]. One feature of ganglioneuroma on MRI is a whorled appearance due to bundles of collagen and Schwann cells that interlace in a characteristic manner [99]. Also, ganglioneuromas often have progressive enhancement pattern on CT that can help distinguishing ganglioneuromas from other adrenal tumors such as ACC and adenomas (Fig. 16) [101]. Because the mean size of adrenal ganglioneuromas is 6.8 cm and they commonly demonstrate heterogeneity and calcification, ganglioneuromas are usually managed surgically [102].

Ganglioneuroblastoma is a malignant lesion that has a variable CT appearance ranging from solid heterogeneous masses to predominantly cystic ones. The variable CT appearance is likely related to differences in the percentage of ganglion cells constituting the tumor relative to other

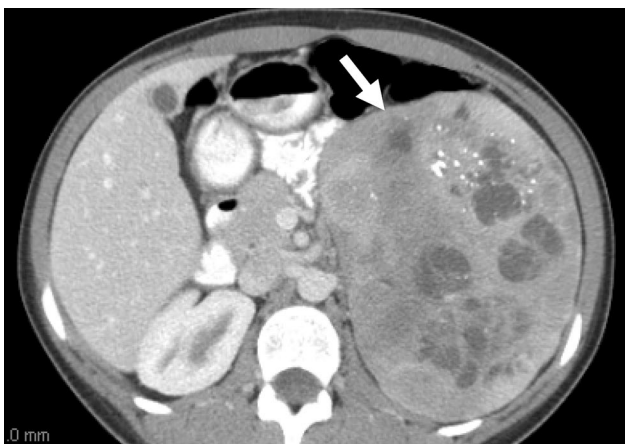

Fig. 16 A 23-year-old female patient with a palpable left upper quadrant abdominal mass. Axial contrast-enhanced abdominal CT shows a large left adrenal mass (white arrow) with areas of necrosis and coarse calcifications. The mass was biochemically inactive. Based on imaging features, ACC was suspected. The mass was pathologically proven ganglioneuroma

immature elements [99, 103]. By MRI ganglioneuroblastoma usually displays low T1 and heterogeneous T2 signal intensity and marked rapid contrast enhancement [104].

Adrenal hemorrhage and pseudocyst

Adrenal hemorrhage may be due to traumatic or non-traumatic etiologies. Non-traumatic causes include coagulopathy, sepsis, and venous thrombosis. Adrenal hemorrhage appears as an oval or rounded mass with surrounding fat-stranding and high CT attenuation value ranging from 50 to 90 HU. The size and attenuation value of adrenal hematoma decrease over time, and usually the lesion will eventually completely resolve (Fig. 17). Hemorrhage with an underlying mass should be suspected in cases with no risk factors for traumatic or non-traumatic hemorrhage, as ACC and other solid adrenal masses can present with hemorrhage. MRI with subtraction images can be essential for the detection of the enhancing solid component or for detecting venous thrombosis that might predispose to hemorrhage [105].

An adrenal pseudocyst is a sequela of chronic adrenal hemorrhage, typically appearing as a cystic structure with thin wall [106]. However, a pseudocyst may appear as a mixed solid and cystic mass or a pure solid mass by CT, which might be confused with adrenal tumors. The CT appearance depends on the age of the hematoma. The presence of solid enhancement can point to a neoplastic etiology rather than pseudocyst [107]. Other features concerning for malignancy within a cystic lesion include large size, heterogeneous appearance, and the presence of calcifications or central necrosis. These features may necessitate surgical excision [108].

Adrenal hemangioma

Hemangiomas are tumors arising from the endothelial lining of blood vessels, and the majority of these lesions involving the adrenal gland are incidentally discovered. Peripheral patchy enhancement with centripetal filling is a typical imaging feature of hemangioma by both CT and MRI, and when this is absent, hemangiomas may be confused with other masses [109]. Marked T2 hyperintensity and focal T1 hyperintensity due to hemorrhage and calcifications might be seen in hemangiomas but are nonspecific [110].

Treatment options and surgical resection

Surgical resection is the mainstay of treatment for localized disease (Stage I–III), with a 5-year survival rate of 55% in case of complete resection [111]. Open adrenalectomy is the standard surgical technique used for large lesions (> 6 cm) or for lesions with suspected loco-regional infiltration. This decreases the risk of capsular rupture and peritoneal

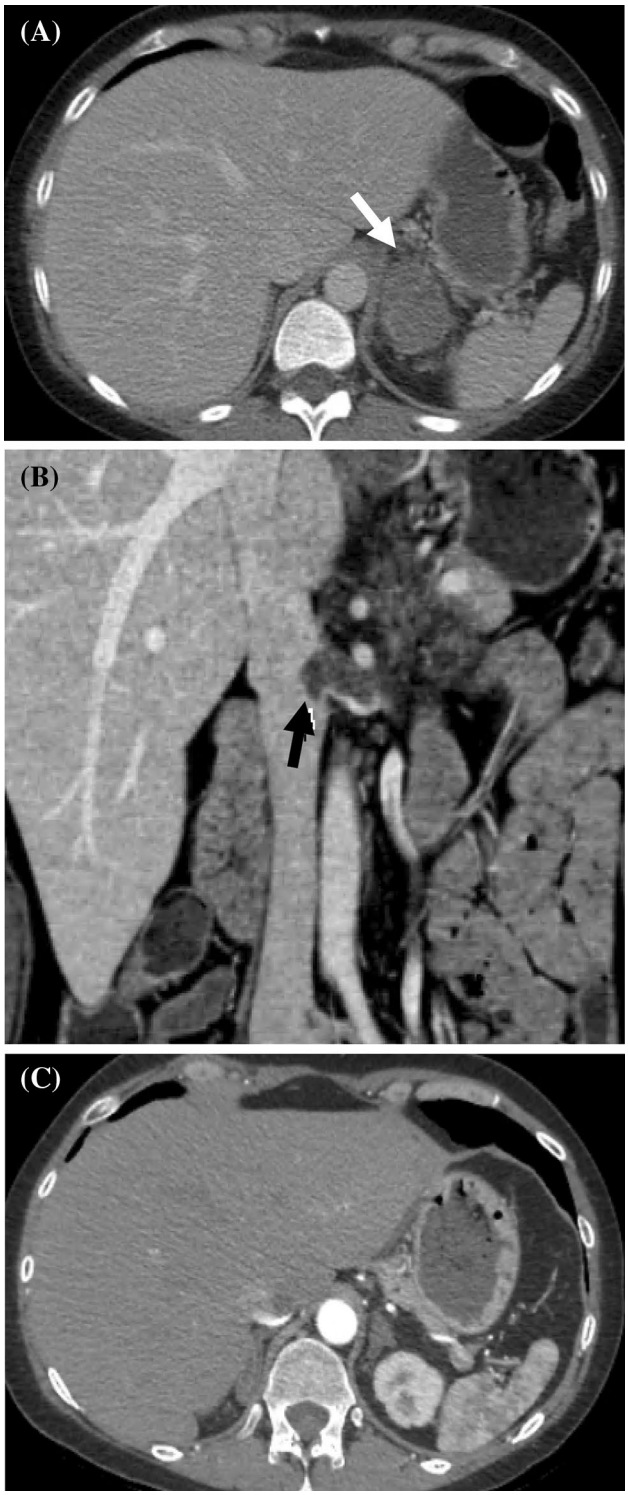

Fig. 17 A 50-year-old female patient with left flank pain. **a** Axial contrast-enhanced abdominal CT shows a left non-enhancing adrenal mass (white arrow). **b** Coronal contrast-enhanced abdominal CT shows left renal vein occlusive thrombus (black arrow). **c** Follow-up abdominal CT obtained 3 months later shows complete resolution of the previously noted left adrenal mass, consistent with adrenal hematoma

carcinomatosis and allows adequate resection of the tumor to avoid local recurrence. Laparoscopic resection can be considered for tumors less than 6 cm in size, especially when performed by experienced surgeons. Lesions with extensive infiltration of the surrounding tissues require en bloc resection of the tumor and the adjacent invaded organs [112].

Vascular invasion is not a contraindication to surgery, and complete surgical resection with free resection margin remains the only curative option for those patients. However, vascular invasion adds complexity to the surgical approach. The extent of tumor thrombus and its extension to vascular and cardiac structures are best assessed with MRI and are essential for planning the surgical approach. Extension of thrombus to the IVC and other vessels requires extensive thrombectomy, and potentially cardiopulmonary bypass if cavoatrial extension is seen [113].

Adjuvant therapy

Due to the high risk of local recurrence even with complete resection, adjuvant therapy might be needed. The most commonly used adjuvant therapy is mitotane which is an adrenolytic drug. There is a controversy in the literature regarding the efficacy of mitotane in preventing local recurrence. However, the current guidelines recommend the use of mitotane in patients with high risk of recurrence, including stage III disease or a high proliferation index (Ki67 greater than 10%) [114].

A large retrospective cohort study in Italy and Germany reported prolonged overall survival and disease-free survival in patients receiving adjuvant mitotane after surgical resection, suggesting the efficacy of mitotane in improving clinical outcomes [115]. A more recently updated series of 152 ACC patients who deemed at high risk of recurrence and adjuvant mitotane was associated with improved overall survival and prolonged recurrence-free survival [116].

Systemic therapy

Patients with advanced metastatic disease at the time of diagnosis have poor outcomes, and management is centered on the use of palliative systemic therapy. Mitotane is used alone or in association with systemic chemotherapy for that purpose [111].

Targeted therapies

There are multiple ongoing clinical trials and evolving targeted therapies, which aim to combat metastatic disease through the targeting of molecular pathways involved in the pathogenesis of ACC. These novel agents include drugs that target the WNT signaling pathway, vascular endothelial growth factor inhibitors, IGF-II inhibitors, and other tyrosine kinase inhibitors. Although targeted therapies showed promising preclinical results, the clinical results have been disappointing. This could be explained by the multiple molecular pathways involved in the pathogenesis of ACC, which may make different drug classes effective in only a small subgroup of patients. Ongoing trials and patient-directed tumor analysis may yield results in the future [25].

Surveillance guidelines

Due to the high recurrence rate of ACC, close follow-up is recommended even after complete resection. Follow-up with abdominal CT or MRI and CT of the chest every 3 months for the first 2 years is recommended. Additional monitoring of steroid hormones level is essential, especially in hormonally active tumors to detect early recurrence. After 2 years of follow-up, the interval may be increased to every 6 months for 5 years [5, 117]. Approximately 90% of cases recur during the first five years after resection, so there is no clear recommendation for patient surveillance after 5 years. Annual follow-up for another 5 years might be adapted according to the clinical situation and the judgment of the physician [10].

Surveillance for more advanced disease should be tailored according to the prognostic factors, ongoing treatment, and expected treatment efficacy and is generally recommended every 2–3 months. There are no guidelines for patients with advanced metastatic disease undergoing only palliative therapy [10].

Conclusion

ACC is a rare tumor with a dismal prognosis and is best managed using a multidisciplinary approach. Knowledge of the various imaging features of ACC and differentiating it from other lesions is of utmost importance to improve treatment outcomes. Additionally, adequate staging with precise delineation of tumor extension and infiltration into surrounding tissues is the cornerstone in guiding a treatment plan. Different imaging modalities including CT, MRI, and PET are complementary to each other in evaluating adrenal masses and can be tailored according to the clinical scenario. Pathological markers such as the Weiss score and Ki67 index are important diagnostic and prognostic indicators for ACC.

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