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CONTINUING EDUCATION– ENDOCRINE TUMORS

Evaluation, Staging, and Surgical Management for Adrenocortical Carcinoma: An Update from the SSO Endocrine and Head and Neck Disease Site Working Group

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ABSTRACT This is the first of a two-part review on adrenocortical carcinoma (ACC), a rare and aggressive malignancy that often presents at an advanced stage. Most patients present with symptoms related to cortisol and/or androgen excess. Appropriate biochemical evaluation and imaging is important in assessing the extent of disease, operative planning, and oncologic surveillance for patients with ACC. For patients with locoregional disease, potential cure requires margin-negative resection, and accumulating evidence suggests that regional lymphadenectomy should be performed. Although laparoscopic adrenalectomy is reported by some to be adequate for localized ACC, open resection in the hands of an experienced adrenal surgeon is the gold standard for operative management of this disease. Cure is rare following disease relapse, however select patients with severe symptoms related to hormone excess or pain may benefit from resection of local or distant recurrence. For best oncologic outcomes, it is recommended that all patients with ACC be treated at centers with multidisciplinary expertise in management of this rare and aggressive malignancy.

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Adrenocortical carcinoma (ACC) is a rare malignancy with an annual incidence of approximately 0.5–2 cases per million people.[1,2] It often presents as locally advanced or metastatic disease.[3] Optimal management for locoregional disease includes resection with or without adjuvant therapy. However, recurrence rates remain high and systemic therapy options for metastatic disease are limited. Mechanisms driving ACC carcinogenesis have been extensively studied and alterations in several molecular pathways have been described.[4] Unfortunately, therapeutic targeting of these pathways has yielded minimal progress in improving outcomes. The current two-part review is authored by members of the Society of Surgical Oncology (SSO) Endocrine and Head and Neck Disease Site Working Group and is intended to provide a comprehensive and contemporary overview on evaluation, staging, and surgical management for ACC; detail current evidence regarding adjuvant therapy and ongoing investigation in therapeutic strategies for advanced disease; and highlight the importance of considering hereditary syndromes in patients with ACC. Of note, this is not a consensus guideline or a position statement by the SSO.

PRESENTATION, EVALUATION, AND STAGING

Presentation and Biochemical Evaluation

Approximately two-thirds of ACC patients will have excess secretion of steroid hormones, with the majority demonstrating overt clinical symptoms.[4,5] Cortisol is the most common hormone secreted, with up to 40% of

patients having Cushing's syndrome.[6] However, secretion of a single steroid is uncommon and in approximately 30% of patients there is overproduction of glucocorticoids in combination with sex steroids.[4–6] Hyperaldosteronism is rare in ACC, occurring in ≤ 2% of cases.[4,5] Approximately one-third of patients with ACC will present with fever or local symptoms such as pain, fullness, or a palpable mass.[7]

Recommendations for biochemical evaluation of adrenal nodules and 'incidentalomas' are well described.[8–10] In general, screening for cortisol overproduction, pheochromocytoma, and aldosteronoma (if hypertensive and/or hypokalemic) should be performed for newly detected adrenal masses, while testing for sex hormones should be reserved for patients with virilizing features or clinical and imaging findings consistent with ACC (Table 1). When ACC is suspected, a thorough hormonal profile should be obtained to help guide postoperative management with regard to necessary hormone replacement therapy and to serve as surrogate tumor markers during oncologic surveillance.

Imaging

Appropriate imaging is important in distinguishing benign lesions from potentially malignant lesions, and, for patients with ACC, is critical for clinical staging and surgical planning (Table 2).

Computed tomography (CT) is most commonly used and most centers have 'adrenal protocols' with image acquisition in the precontrast, portal venous (60 s), and delayed postcontrast (10–15 min) phases. Precontrast attenuation and contrast washout patterns of adrenal neoplasms are well characterized,[11] and when considered with other radiographic features such as size, internal appearance (homogenous vs. heterogeneous), margins (smooth vs. irregular or infiltrative), and lymphadenopathy, yield a wealth of information regarding the likely diagnosis. An adrenal mass with a precontrast density of < 10 Hounsfield units (HU) is almost invariably benign.[12] In masses with intermediate precontrast density, the percentage of contrast washout calculated after portal venous and delayed postcontrast imaging has been reproducibly demonstrated to distinguish adenomas from adrenal metastases, ACC, and pheochromocytomas. Washout can be measured in two ways—as absolute percentage washout (APW) or relative percentage washout (RPW); greater than 60% APW or 40% RPW is consistent with an adenoma.[8,11]

On CT, ACC is typically identified as a large mass with a heterogeneous internal appearance and indistinct margins (Fig. 1). Invasion into surrounding viscera or extension of

TABLE 1 Recommended imaging and biochemical evaluation for patients with suspected adrenocortical carcinoma[8–10,73]

Biochemical evaluation
Glucocorticoid excess (at least one of the first four tests)
Low-dose dexamethasone suppression test
24-h urinary free cortisol
Extended (2-day) low-dose dexamethasone suppression test
Late night salivary cortisol test
Basal plasma ACTH (in adjunct to one of the above tests)
Sex steroids and precursors
Serum DHEA-S
Serum 17-OH-progesterone
Serum androstenedione
Serum 17β-estradiol (only in men and postmenopausal women)
Mineralocorticoid excess
Serum potassium
PAC/PRA (only in patients with hypertension and/or hypokalemia)
Pheochromocytoma testing (at least one of two tests)
Plasma meta- and normetanephrines
24-h urinary catecholamines, metanephrines, VMA
Imaging
CT chest (evaluate for pulmonary metastases)
CT abdomen and/or MRI (adrenal protocol)
FDG-PET/CT reserved for indeterminate sites of potential metastases

ACTH adrenocorticotropic hormone, *DHEA* dehydroepiandrosterone, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *VMA* vanillylmandelic acid, *CT* computed tomography, *MRI* magnetic resonance imaging, *FDG* 18-fluorodeoxyglucose, *PET* positron emission tomography

TABLE 2 Comparison of features distinguishing benign adenoma from adrenocortical carcinoma

Characteristics	Adenoma	ACC
Imaging		
Size	Typically < 4 cm[74,75]	Size > 4 cm has > 90% sensitivity in detecting malignancy[75]
		An increase in tumor size during interval imaging is predictive of malignancy[76]
Borders	Smooth	Typically irregular and infiltrative
Density and washout characteristics	Lipid-rich adenomas	May have lipid-rich areas, but not typically uniform throughout the tumor
	< 10 HU on non-contrasted CT	May have washout characteristics similar to lipid-poor adenomas, but large size and infiltrative borders help distinguish. May have peripheral rim enhancement[13]
	< 20% decrease in signal intensity on chemical shift MRI[13]	On MRI, often have heterogeneous T1- and T2-weighted signal intensity
	Lipid-poor adenomas	
	Greater than 60% APW or 40% RPW on adrenal protocol CT	
	No decrease in signal intensity on chemical shift MRI[13]	
Internal features	Typically homogeneous	Often heterogeneous and may have areas of internal necrosis and/or hemorrhage
Venous thrombus	Never present	May be present
Hormonal function	Most commonly non-functional (~ 85%)[75]	Most commonly functional (~ 60%)
	If functional, only hypersecretion of one hormone	May secrete multiple hormones

ACC adrenocortical carcinoma, *HU* Hounsfield units, *CT* computed tomography, *MRI* magnetic resonance imaging, *APW* absolute percentage washout, *RPW* relative percentage washout

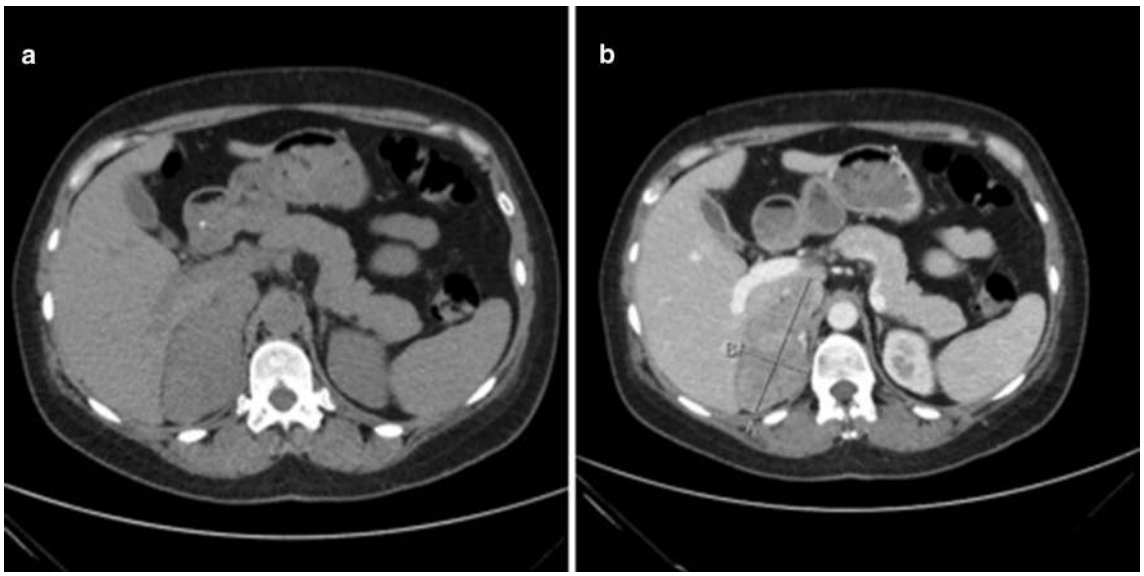

FIG. 1 **a** Precontrast and **b** postcontrast computed tomography in a 45-year-old female with Cushing's syndrome and adrenocortical carcinoma. Imaging reveals a heterogeneously enhancing right adrenal mass with irregular margins and tumor thrombus extension into the inferior vena cava

the tumor thrombus into the inferior vena cava (more common for right-sided tumors) (Fig. 1) or the renal vein (more common for left-sided tumors) should be assessed. In addition, CT of the chest should be performed to evaluate for potential pulmonary metastases.

On contrast-enhanced magnetic resonance imaging (MRI), ACC is typically heterogeneous secondary to areas of internal necrosis and hemorrhage, leading to variable brightness on T1- and T2-weighted images.[13] MRI may provide more detailed information regarding the extent of

locoregional or vascular invasion if CT is equivocal. Chemical shift MRI, which uses resonant frequencies of fat and water to assess intracellular fat, will demonstrate a loss of signal intensity on out-of-phase imaging for lipid-rich adenomas. Compared with conventional T1- and T2-weighted MRI, this technique has been shown to yield better diagnostic accuracy in distinguishing adenomas from non-adenomas.[13,14]

The utility of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT for patients with ACC is not well defined. FDG-PET/CT is not recommended in patients without a prior history of malignancy and CT findings characteristic of a benign adenoma (< 4 cm, well-circumscribed, < 10 HU on non-contrast phase, and/or characteristic washout percentages). In patients with a prior history of an extra-adrenal malignancy with a proclivity for adrenal metastases such as lung, renal, breast, colon, or melanoma, PET/CT can be useful in characterizing an adrenal mass along with other potential sites of metastases.[15] For patients without a prior history of malignancy, FDG-PET/CT should be reserved for indeterminate characteristics on CT (≥ 10 HU precontrast density and/or equivocal washout characteristics). In this setting, using a tumor maximum standardized uptake value (SUVmax)/liver SUVmax cut-off of > 1.5–1.8, FDG-PET/CT has been shown to detect malignant lesions with reasonable sensitivity (86–87%), specificity (84–86%), positive predictive value (57–85%), and negative predictive value (86–97%)[16,17] For a patient with a clinical diagnosis of ACC based on presentation and CT or MRI, FDG-PET/CT may help characterize potentially involved regional lymph nodes or indeterminate lesions representing potential sites of distant metastases. Otherwise, it is unlikely to provide additional information for preoperative planning, and is not always necessary in the initial evaluation. In general, FDG-PET/CT should be used selectively in the evaluation of patients with indeterminate adrenal masses or ACC.

Biopsy

In general, biopsy of an adrenal mass is not required or advisable since characterization of adrenal masses can typically be obtained with a history and physical examination, appropriate imaging, and biochemical evaluation. Biopsy has relatively poor sensitivity in detecting ACC.[18] While case reports of biopsy needle track seeding of ACC exist,[19,20] these events are rare and should not influence the decision to perform a biopsy. Biopsy might be advisable in ACC if the mass is unresectable or 'borderline resectable' based on locoregional invasion, and a tissue diagnosis is needed to initiate non-surgical therapy. Biopsy may also be indicated when there is a prior cancer history and concern for an adrenal metastasis. When biopsy is performed, it should be preceded by biochemically ruling out pheochromocytoma.

Staging

The most widely used staging systems for ACC are the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) and European Network for the Study of Adrenal Tumors (ENSAT) systems (Table 3). The AJCC/UICC system has been in use the longest, however the ENSAT system has become more widely used due to its apparent superiority.[21,22] A comparison of the staging systems is shown in Table 1. In addition, because factors such as age, tumor grade, margin status, and symptoms at diagnosis have been demonstrated to further refine prognosis, other novel staging systems been proposed.[23,24]

SURGICAL THERAPY

Margin-negative (R0) resection remains the only curative option for ACC.[25–28] The importance of R0 resection is emphasized by a recent study of 165 patients from 13 US academic institutions who underwent curative-intent adrenalectomy.[29] Margin-negative resection was achieved in 76% of patients and margin status was an independent predictor of overall survival. The 5-year overall survival for R0 versus R1 resection was 64.8% and 33.8% ($p < 0.001$), respectively. Similarly, the 5-year recurrence-free survival for R0 and R1 resection was 30% and 14% ($p < 0.03$), respectively. Using the National Cancer Database (NCDB), two other studies have demonstrated that margin-positive resections are associated with decreased overall survival.[29,30] Other single-center studies failed to show that margin status influenced survival, but confirmed its negative effect on recurrence.[3,31]

Since complete resection is important for survival, it follows that surgical approach should be optimized towards achieving this goal. The authors consider open adrenalectomy (OA) the procedure of choice for ACC as it allows for complete *en bloc* resection and lymphadenectomy.[32–35] This is particularly applicable to stage I/II ACC (AJCC or ENSAT) when cure is still possible. Early reports on the use of laparoscopic adrenalectomy (LA) for ACC cautioned about tumor capsule rupture and carcinomatosis,[26,36–38] but other retrospective series have suggested LA can be a safe approach for non-invasive, smaller (< 10 cm), ENSAT stage I/II ACC.[39,40] There are no randomized controlled studies evaluating LA versus OA. Selected retrospective case–control series are listed in Table 4. Miller et al.[41] observed increased margin-positive resections, tumor spillage, and recurrence, along with

TABLE 3 Comparison of the AJCC[77] and ENSAT staging systems

	Stage I	Stage II	Stage III	Stage IV
AJCC/UICC	T1, N0, M0	T2, N0, M0	T1-2, N1, M0 or T3, N0, M0	Any T, any N, M1 or T3, N1, M0 or T4, any N, M0
ENSAT	T1, N0, M0	T2, N0, M0	T1-2, N1, M0 or T3-4, N0-1, M0	Any T, any N, M1

T1: $\leq$ 5 cm and confined to the adrenal gland

T2: $>$ 5 cm and confined to the adrenal gland

T3: Tumor of any size with local invasion, but not invading adjacent organs

T4: Tumor of any size with local invasion into adjacent organs/great vessels

N0: No regional nodal metastasis

N1: Positive regional nodal metastasis

M0: No distant metastasis

M1: Distant metastasis

AJCC American Joint Committee on Cancer, *ENSAT* European Network for the Study of Adrenal Tumors, *UICC* Union for International Cancer Control

lower survival, for stage II patients undergoing LA. Only 15% of resections were performed at their center. Similarly, Cooper et al.[37] reported a higher incidence of positive margins and peritoneal recurrence in patients undergoing LA for ACC. Other multi-institutional series showed no difference in survival by approach. However, in several of these reports, LA was utilized for smaller, highly selected ACC patients, and, in two of the largest series, margin positive resections were excluded.[39,40] Three meta-analyses have evaluated the controversy. Sgourakis et al. reported that OA provides better survival rates at 5 years,[42] while Autorino et al. found no difference in overall recurrence or cancer-specific mortality, but carcinomatosis was higher in the LA group[43] and they concluded that oncologic principles should not be compromised by minimally invasive approaches. Lastly, Langenhuijsen et al.[44] found no difference between approaches and concluded that LA is as effective as OA for localized ACC, as long as oncologic principles are respected.

Lack of experience with ACC resection can lead to tumor rupture and incomplete resection (R1/R2/missed lymph nodes) regardless of approach. Several reports have demonstrated higher rates of radical and complete tumor resection and lower rates of positive margins when ACC is initially treated at centers with expertise in treating this disease.[3,25,34,45–47] At these centers, overall and disease-specific survival were superior than at centers with less experience. Furthermore, treatment at high-volume centers is associated with higher rates of adjuvant chemotherapy.[48,49]

Regional lymphadenectomy (RLND) for staging and potential therapeutic benefit is standard in oncologic resection for most intra-abdominal malignancies, however its role in ACC has historically been ill-defined.[35] As expected, nodal metastases have been demonstrated to negatively impact survival in patients with resected ACC.[50,51] A challenge in understanding the true impact of RLND for ACC is the lack of well-defined anatomic boundaries, resulting in significant variation in the extent of lymphadenectomy performed. This is highlighted by the variety of definitions used to describe RLND for ACC in both population-based and institutional series evaluating its influence on survival.[51–55] Furthermore, reported rates of performing RLND in these series is low, ranging from 6 to 33%. In a report using the Surveillance, Epidemiology, and End Results (SEER) database, Tran et al.[51] found lymphadenectomy was associated with improved survival on univariate analysis for patients with AJCC T4 tumors. However, subsequent data generated from analyses of SEER[53,54] showed no difference in disease-specific or overall survival in patients undergoing lymph node dissection for resected ACC. In contrast, evaluation of 283 patients from the German ACC Registry found RLND resulted in a reduced risk of tumor recurrence (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.43–0.98, $p = 0.42$) and disease-related death (HR 0.54, 95% CI 0.29–0.99, $p = 0.049$),[56] and recommended anatomic resection based on previously described adrenal lymphatic drainage patterns.[57] Similarly, a collaborative study of 13 academic centers in the US found that 'intended lymphadenectomy' as described by the operative surgeon resulted in improved OS (HR 0.17, 95% CI 0.05–0.61, $p = 0.006$) when controlling for adverse factors. The homogeneity of patient selection, granularity of data, and consistency in outcomes in these two multi-institutional studies seems to yield credence to routine performance of an anatomically based RLND for improved staging and potential survival benefit when performing curative intent resection for ACC.

TABLE 4 Selected series evaluating outcomes of open versus laparoscopic adrenalectomy for adrenocortical carcinoma

Study	*N*	LA/OA	Median tumor size, cm (LA/OA)	AJCC or ENSAT stage, % (LA/OA)	Tumor rupture, % (LA/OA)	Positive margin, % (LA/OA)	OS, months (LA/OA)	Recurrence, months (LA/OA)	Comments
*Lee et al. 2017[78]	201	47/154	5.5/10.9 $p = 0.001$	AJCC T1-2 75%/44% $p = 0.001$	8.8%/9.4% $p = 0.999$	27.5%/28% $p = 0.953$	Median 91/53.9 $p = 0.289$	Median DFS 14.3/9.8 $p = 0.174$	Conversion 19%, AJCC T1-4
Fossa et al. 2013[79]	32	17/15	8/13 $p = 0.002$	ENSAT I/II 76%/46% 0.06	29%/13%	29%/20% $p = 1.0$	Median 103.6/36.5 $p = 0.22$	Median PFS 15.2/8.1 $p = 0.06$	Stage I/II ENSAT 12% conversion, pattern of recurrence similar LA vs. OA
Mir et al. 2013[80]	44	18/26	7/13 $p = 0.001$	AJCC I/II 82%//35%	NR	39%/38% $p = NS$	2-year 58%/54% $p = 0.6$	2-year RFS 39%/60% 0.7	Cancer-specific deaths 59%/73% $p = 0.361$
Cooper et al. 2013[37]	92	46/46	8/12.3 $p \leq 0.0001$	AJCC T1,2 63%/56% $p = 0.1$	NR	28.3%/8.7% $p = 0.01$	Median 54/110 $p = 0.07$	Median RFS 11/20 $p = 0.005$	Peritoneal recurrence 54%/19% $p = 0.006$ R2 excluded
Miller et al. 2012[41]	156	46/110	7.4/12 NR	AJCC I/II 72%/50%	NR	Spill/positive margin 30%/16% $p = 0.04$	Stage II only 51/103 $p = 0.002$	Time to recurrence, months 17.6/52.9 $p = 0.001$	OS longer for OA stage II, initial resection at center in only 15%
*Lombardi et al. 2012[39]	156	30/126	Mean 7.7/9 $p = 0.147$	All ENSAT stage I/II	Excluded	Excluded	Median 108/60 $p = 0.2$	Median RFS 72/48 $p = 0.120$	More LA patients had incidentalomas
*Brix et al. 2010[81]	152	35/117	6.2/8 $p = 0.001$	ENSAT I/II 89%/68% $p = 0.001$	9%/15% $p = 0.4$	6%/12% $p = 0.45$	Not different $p = 0.55$	Not different $p = 0.82$	Carcinomatosis 3% each
Porpiglia et al. 2010[40]	43	18/25	9/10.5 $p = 0.39$	All ENSAT I/II	Excluded	Excluded	Median not reached	Median RFS 23/18 $p = 0.8$	Resection at the center in only 23%

LA laparoscopic adrenalectomy, *OA* open adrenalectomy, *AJCC* American Joint Commission on Cancer, *ENSAT* European Network for the Study of Adrenal Tumors, *OS* overall survival, *DFS* disease-free survival, *PFS* progression-free survival, *RFS* recurrence-free survival, *NR* not recorded, *NS* non-significant

* indicates multi-institutional study

Due to limited efficacy and associated toxicity with currently available systemic therapy for ACC, it is critical to appreciate the role of resection of locally advanced and recurrent or metastatic disease. Although cure is rarely achieved in these circumstances, resection may offer survival benefit as well as symptom relief in appropriately selected patients. Importantly, pursuit of resection in these patients should be considered on a case-by-case basis and ideally after multidisciplinary evaluation in an experienced center.

Major venous tumor thrombus is present in many patients with T4 tumors, and outcomes of resection in this setting have been evaluated.[58–60] A review of patients at the Mayo Clinic is the only series comparing survival in patients undergoing resection with or without inferior vena cava tumor thrombus. The authors found similar perioperative morbidity and 24-month survival rates; however, survival rates became disparate by 36 months, and 60-month survival in patients with resected tumor thrombus was 0% compared with 40% without.[59]

Several series have evaluated results following the resection of local and distant recurrent disease. Although these are retrospective studies with inherent selection bias, the collective experience consistently demonstrates that patients with a disease-free interval of at least $\geq$ 1 year, and the ability to achieve margin-negative resection, offers median overall survival $>$ 5 years.[61–65] Moreover, survival outcomes appear similar for resection of both local and/or distant recurrence. In the setting of a short disease-free interval or inability to remove all recurrent disease, resection of recurrence yields a median OS of 1–3 years.[61–64] Evaluation of resection for organ-specific metastases, such as pulmonary[66,67] and hepatic,[68,69] has also been performed. These studies demonstrate the ability to perform such resections safely, with repeat metastasectomy in many cases, and consequent durable survival benefit in select patients. In an effort to better define the selection of patients most likely to achieve a survival benefit from resection of recurrent ACC, a multi-institutional analysis from 13 US centers found multifocal recurrence, disease-free interval $<$ 1 year, and extrapulmonary distant metastases were independent predictors of poor survival.[70]

For patients presenting with synchronous distant metastases, the role of surgery is limited. A combined series from the Mayo Clinic and MD Anderson Cancer Center evaluated 27 patients operated for synchronous metastases.[71] Patients having R0 resection had a median overall survival of 860 days, compared with 390 days for R2 resection. Notably, only 11 patients (40%) in this series were able to have margin-negative resection. Eight patients receiving preoperative therapy with mitotane, etoposide, doxorubicin, and cisplatin, as well as one patient receiving mitotane only, were found to have a trend towards improved 1, 2, and 5-year OS compared with those not receiving neoadjuvant therapy. Available data suggest the majority of patients receiving neoadjuvant therapy will have a partial response or disease stability.[71,72] In these high-risk patients, a course of preoperative therapy to avoid operating patients with rapidly progressive disease seems reasonable.

CONCLUSIONS

ACC should be suspected in patients with large, heterogeneous, irregular adrenal masses, particularly if there is evidence of excess cortisol and/or androgen hypersecretion. A surgical approach that achieves complete resection and removal of involved lymph nodes is recommended. Optimal oncologic outcomes appear to occur when patients are cared for at centers with multidisciplinary expertise in this rare and aggressive malignancy.

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