INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare malignancy with an annual incidence of 1 to 2 cases per million individuals. Notwithstanding, frequent presentation with sequelae of steroid precursor overproduction, proclivity for aggressive local growth, early metastasis and recurrence, and the scarcity of effective systemic treatment options contribute to a substantial burden of disease. Women are more affected than men, at a ratio of 1.5:1. Although ACC affects individuals of all ages, cases are clustered
in early childhood or middle age. Most cases are seemingly sporadic; however, ACC may arise in association with hereditary syndromes, including multiple endocrine neoplasia-1 and Li-Fraumeni syndrome. Overall prognosis is poor; estimates of 5-year survival range from 30% to 50%; metastatic disease is associated with a median survival of less than 1 year. Surgery is the cornerstone of therapy for localized disease and has a role in selected recurrent cases. Although an association between complete resection with negative margins and survival has been reproduced in numerous series, the frequent presentation with at least locally advanced disease and presence of major vascular invasion or direct invasion of contiguous structures undermine effective surgical therapy in many cases. Moreover, presence of occult micrometastatic disease at the time of presentation is confirmed by frequent distant failure after apparent negative margin resection. Owing in part to its low incidence, data for many accepted elements of therapy are limited or nonexistent. This review critically considers the existing evidence for elements of the evaluation and treatment of patients with ACC, with a particular focus on surgical management.

WHAT IS THE APPROPRIATE DIAGNOSTIC AND IMAGING WORKUP FOR PATIENTS WITH SUSPECTED ADRENOCORTICAL CARCINOMA?

The presentation of ACC is highly variable. Smaller nonfunctional ACCs are sometimes identified incidentally. Approximately 50% to 60% of ACCs are functional and present with signs or symptoms of hormone excess. As with all tumors of the adrenal gland, directed laboratory testing and high-resolution imaging are critical and allow appropriate management. The former should include serum metanephrines to exclude pheochromocytoma. Glucocorticoid excess may be discerned through measurement of levels of serum cortisol and plasma adrenocorticotropic hormone or 24-hour free urinary cortisol; a more definitive diagnosis may require low-dose dexamethasone suppression. Levels of sex steroids and steroid precursors, including dehydroepiandrosterone sulfate (DHEA-S), 17-OH progesterone, androstenedione, testosterone, and 17-β-estradiol (in men and postmenopausal women), may be elevated in serum. Mineralocorticoid excess may be driven by glucocorticoid-mediated mineralocorticoid receptor activation in the occasional patient with hypercortisolism and is detected through measurement of the plasma aldosterone/renin ratio. Urinary steroid metabolomic profiling has emerged as a promising diagnostic tool, but it has yet to be validated in larger prospective multicenter series.

Computed tomography (CT) and MRI are similarly effective at discriminating between benign and malignant adrenal tumors and identifying metastases. The choice of one imaging study over another is largely a question of institutional preference with some caveats: (1) CT is less expensive and (2) MRI is preferable when pheochromocytoma is suspected because of the purported risk of a hypertensive crisis after intravenous infusion of iodinated CT contrast. Hounsfield units less than 10 on unenhanced CT, rapid washout at 15 minutes on delayed contrast-enhanced CT, or signal intensity loss using opposed-phase MRI are consistent with a benign tumor. ACCs are typically heterogeneous with irregular margins and irregular enhancement of solid components. With ACC, invasion of adjacent structures or extension into the inferior vena cava (IVC), locoregional lymph node metastases, and distant metastases may be seen. PET with fluorodeoxyglucose F18 may have additional sensitivity in identifying metastases. Use of radiolabeled mitomide, highly specific for adrenal cortical cells via targeted binding to both 11β-hydroxylase and aldosterone synthase, for either PET- or single-photon emission CT–based functional imaging is another emerging technique with high sensitivity and specificity for ACC.
Percutaneous biopsy of a potentially resectable suspected ACC is rarely indicated. It is infrequently helpful owing to poor sensitivity and may result in complications (eg, bleeding and pneumothorax). An increased risk of biopsy site or peritoneal recurrence is often invoked but is largely unproven. In the rare circumstance when biopsy is undertaken (eg, to discriminate a metastasis from a primary adrenal malignancy or in anticipation of neoadjuvant therapy), the diagnosis of pheochromocytoma must first be excluded.

WHAT ARE THE PATHOLOGIC DETERMINANTS OF MALIGNANCY? WHAT FACTORS ARE PROGNOSTIC IN RESECTED ADRENOCORTICAL CARCINOMA?

Histopathologic differentiation between benign and malignant adrenocortical tumors is often challenging. Given that the definitive criteria for malignancy are distant metastasis and local invasion, Weiss proposed a system encompassing 9 morphologic criteria associated with locally recurrent and metastatic adrenocortical tumors (Box 1). The subjective identification of 3 of these 9 criteria represents the current standard in establishing adrenocortical malignancy. This classification system, although simple and prognostic, has significant limitations: (1) the criteria do not perform well in the identification of special variants (eg, myxoid, sarcomatoid, pediatric, and oncocytic) and (2) their diagnostic accuracy is lower when applied by nonexpert pathologists; subjectivity of assessment generates substantial interoperator variability, which limits diagnostic reproducibility. Several immunohistochemical markers have emerged as adjuncts to standard histopathologic analysis and may reduce ambiguity (eg, Ki67 proliferation index, steroidogenic factor-1 [SF-1], tumor protein P53, insulin-like growth factor (IGF) 2, cyclin E, reticulin, E3 ubiquitin-protein ligase [MIB-1]). Although promising, these markers have not consistently discriminated ACC from benign adrenal lesions in retrospective studies, and large-scale validation is lacking.

Once malignancy has been established using biochemical, imaging, or pathologic criteria, tumor stage is prognostic of outcome. Although the TNM (tumor, node, metastasis) system from the American Joint Committee on Cancer (AJCC)/Union for...
International Cancer Control (IUCC) was introduced in 2004, the European Network for the Study of Adrenal Tumors (ENSAT) classification has emerged as a more discerning predictor of cancer-specific mortality risk (Table 1). Although the two systems classify stage I and II tumors identically (ie, node-negative tumors <5 cm or >5 cm, respectively), ENSAT stage III tumors are defined by the presence of positive lymph nodes, infiltration of periadrenal tissue and/or adjacent organs, or venous (ie, IVC or renal vein) tumor thrombus; stage IV ACC includes patients with distant metastasis only. In 492 patients from the German ACC registry, this modification yielded a stage-stratified 5-year disease-specific survival of 82% (stage I), 61% (stage II), 50% (stage III), and 13% (stage IV). The prognostic superiority of the ENSAT, compared with the AJCC/UICC, classification was corroborated in an independent North American cohort of 573 patients. Further improvements to the prognostic value of the ENSAT system, such as addition of tumor grade or molecular markers (eg, SF-1), have been advocated and may be on the horizon.

Beyond ENSAT/AJCC tumor stage, completeness of resection (ie, R0 margin status) is a dominant contributor to disease-free and overall survival in resected ACC. In a retrospective study of 113 patients, patients undergoing complete primary resection demonstrated significantly improved median (74 vs 12 months) and 5-year actuarial survival (55% vs 5%) compared with those undergoing incomplete resection. In an analysis of 3982 patients with ACC from the National Cancer Data Base (NCDB), R0 resection was associated with a 5-year relative survival rate of 50.4%, compared with rates of 23.2% and 10.8% for R1 and R2 resection, respectively. After adjusting for age, tumor size, grade, nodal involvement, presence of distant metastasis, type of resection, and receipt of multimodality therapy, margin-positive resection remained associated with worse risk-adjusted mortality (hazard ratio [HR], 2.06; 95% confidence interval, 1.74–2.43; P<.0001).

In this and other studies, older age, sex, hormone hypersecretion, poorly differentiated histology, multivisceral resection, and nodal or distant metastasis are also associated with poor prognosis. Tumor size, although firmly entrenched in staging classifications, is inconsistently associated with prognosis. Conversely, pathologic characteristics such as mitotic rate, atypical mitotic figures, intratumor

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**Box 1**

**Weiss criteria**

- High nuclear grade (grade 3 or 4)
- Mitosis 6/50 high-powered field or higher
- Atypical mitosis
- Clear cells 25% or less
- Diffuse architecture 33% surface or more
- Confluent necrosis
- Venous invasion
- Sinusoidal invasion
- Capsular infiltration

The identification of 3 of these 9 criteria represents the current standard in establishing adenocortical malignancy.

hemorrhage, tumor necrosis, and Ki67 index are more reproducibly associated with long-term outcomes.\textsuperscript{28,29} Finally, gene expression profiling has identified molecular signatures (eg, \textit{DLG7}, \textit{PINK1}, and \textit{BUB1B}) predictive of malignancy and survival\textsuperscript{30}; however, prognostic stratification using such techniques have yet to be widely adopted into clinic practice.

**WHAT ARE THE PRINCIPLES OF SURGICAL AND PERIOPERATIVE MANAGEMENT FOR PRIMARY TUMORS? HOW SHOULD PATIENTS WHO HAVE UNDERGONE RESECTION BE SURVEILLED?**

Surgical resection remains the cornerstone of treatment and the only curative modality for patients with localized ACC.\textsuperscript{18} The surgeon’s involvement in the care of these patients should begin in the preoperative setting. In patients with hypercortisolism, perioperative steroid replacement, typically with tapering doses of intravenous hydrocortisone, is recommended to mitigate the risk of adrenal insufficiency following adrenalectomy due to a suppressed contralateral gland.\textsuperscript{31,32} The duration of steroid therapy is dictated by time to recovery of the hypothalamic-pituitary axis.\textsuperscript{33}

Once the decision to proceed with resection has been made, aggressive local surgical control should be attempted to achieve negative resection margins. Unilateral
or bilateral subcostal or J- or L-shaped incisions afford adequate access to sites of potential local invasion and metastatic spread. A thoracoabdominal incision is rarely indicated because of its incident morbidity but may be helpful when concomitant pulmonary metastasectomy is planned (see section “Is there a role for an aggressive surgical approach in locally recurrent or metastatic disease?”). En bloc resection of contiguous or discontinuous periadrenal viscera (eg, kidney, colon, spleen, pancreas, stomach) is often required to maintain capsule integrity and prevent tumor spillage.

A unique consideration during surgical resection of ACC is the potential for intracaval extension and/or tumor thrombus (especially for right-sided lesions), observed in up to 25% of cases. Although local vascular invasion carries a poor prognosis (ie, approximately 30% 3-year overall survival), it is not a contraindication to aggressive surgery per se. Careful preoperative planning is necessary to delineate the location and extent of venous involvement, because the principles of resection vary based on these factors. Tumor thrombectomy in the infrarenal IVC can be achieved by vascular control (via cross-clamping or hepatic vascular exclusion), followed by cavotomy and primary closure or vein resection and reconstruction with or without graft interposition; if tumor extraction is not feasible, the infrarenal IVC can be safely resected with or without replacement. If suprahepatic IVC control is necessary, venovenous bypass is sometimes a useful adjunct. In cases of extension above the diaphragm, or especially into the right atrium, cardiopulmonary bypass may be necessary. Preoperative or intraoperative identification of thrombus in these locations is critical, because clamping of a thrombus-filled IVC can result in tumor thromboembolism, with ensuing hemodynamic instability or tumor dissemination. Management of isolated adrenal vein thrombus (AVT) without caval involvement is laterality specific: (1) for right-sided AVT, resection of a vascular cuff and primary closure of the IVC may be necessary to achieve negative margins; (2) for left-sided AVT, kidney-sparing left renal vein resection may be feasible if the azygous and gonadal venous drainage is intact; if the latter systems are involved, ipsilateral nephrectomy may be necessary (see section “Is there benefit to routine en bloc resection of adjacent organs or aggressive regional lymphadenectomy?”).

Hormone function should be monitored closely in the postoperative setting. As discussed earlier, postoperative adrenal insufficiency is managed with glucocorticoid and mineralocorticoid replacement as necessary, until recovery of the hypothalamic-pituitary axis. Postoperative hypercortisolism, typically observed after R1/R2 resections for hormonally overactive tumors, may be managed with a variety of agents, including metyrapone, aminoglutethimide, ketoconazole, mitotane (see section “What are the current and emerging options for multimodality management of adrenocortical carcinoma?”), mifepristone (glucocorticoid receptor antagonist), or etomoxifene. Sex steroid excess can be controlled with androgen receptor inhibitors bicalutamide or finasteride (in virilizing tumors) or antiestrogen therapies, such as tamoxifen or aromatase inhibitors (in estrogen-producing tumors).

Oncologic surveillance of patients who have undergone resection is recommended for up to 10 years and entails cross-sectional imaging with or without biochemical evaluation, depending on the functional status of the primary tumor. Patients with nonfunctional tumors should be under surveillance with periodic CT or MRI because of the risk for early and frequent recurrence (see section “Is there a role for an aggressive surgical approach in locally recurrent or metastatic disease?”). Patients with steroid-producing ACC should be monitored periodically with steroid tumor markers (eg, cortisol, DHEA-S, androstenedione). An increase in hormone levels may indicate recurrence and/or progression before radiographic detection.
IS THERE BENEFIT TO ROUTINE EN BLOC RESECTION OF ADJACENT ORGANS OR AGGRESSIVE REGIONAL LYMPHADENECTOMY?

Although multivisceral resection for margin clearance is clearly indicated, the role for prophylactic organ resection, particularly nephrectomy, is more equivocal. Although early studies advocated for concomitant nephrectomy to improve oncologic outcomes, this premise has since been challenged. Bellatone and colleagues reported on 140 patients undergoing radical resection for advanced ACC; 22 (15.7%) underwent ipsilateral nephrectomy. The disease-free interval (16.6 vs 22.3 months) and recurrence rates (36.4% vs 37.3%) did not differ significantly between patients undergoing and not undergoing nephrectomy, respectively. In a preliminarily reported study by Porpiglia and colleagues, 20 of 82 (24.4%) underwent ipsilateral nephrectomy during curative-intent adrenalectomy; at a median follow-up of 60 months, disease-free and overall survival did not differ between nephrectomy and nonnephrectomy cohorts. Based on these limited data, routine ipsilateral nephrectomy is not recommended unless obvious renal infiltration by tumor or associated renal vein tumor thrombus is encountered intraoperatively.

Nodal status is not only an integral component of staging but also an important prognostic feature in resected ACC. Despite this, surgical extirpation of regional lymph nodes is infrequently performed in part owing to lack of consensus regarding the optimal extent of regional lymphadenectomy during primary resection. Based on studies from the German ACC registry and NCDB, nodal metastasis is identified in approximately 25% of patients with resected ACC; however, the alarmingly high rates of locoregional failure, up to 85% in some series, despite curative-intent resection; substantially greater rates of nodal positivity, as high as 68%, in autopsy studies; and widely variable survival statistics in patients with presumed node-negative stage II resected ACC (ie, indicating overlooked nodal metastasis in worse performers) suggest that the contribution of surgical understaging to poor long-term outcomes may be underappreciated.

The strongest evidence in support of routine regional lymphadenectomy is derived from a retrospective series of 283 patients who had undergone complete resection from the German ACC registry. In the absence of consensus guidelines defining adequate lymph node dissection (LND), an empiric threshold of 5 or more lymph nodes was chosen to discriminate patients in whom nodes were excised inadvertently from those in whom LND was intended. Using this threshold, only 47 (16.6%) underwent LND during primary resection. Although increased nodal retrieval in these cases may have been self-recommending because of the requirement for more extensive surgery—patients with LND underwent multivisceral resection more frequently and had larger tumors and more locally advanced (ie, ENSAT stage III) disease—removal of at least 5 regional lymph nodes was associated with significant reductions in both risk of recurrence (by 35%) and disease-related mortality (by 46%) despite controlling for age, tumor stage, multivisceral resection, and adjuvant treatment. Despite its methodologic limitations (eg, arbitrary determination of a 5-node LND threshold, lack of knowledge of surgical and/or pathologic quality), the greater than 70% 5-year disease-specific survival in the LND cohort makes a compelling argument for an aggressive surgical approach incorporating regional lymphadenectomy for primary ACC.

The optimal anatomic extent of such nodal dissections remains incompletely understood. Recent efforts to define a systematic approach to regional lymphadenectomy have drawn upon the current anatomic understanding of lymphatic drainage from the adrenal glands, as well as an evolving knowledge of locoregional recurrence patterns.
following complete resection. A recent report suggested that first-order drainage pathways from the adrenals encompass renal hilar nodes, nodes associated with the celiac axis, and ipsilateral para-aortic and/or paracaval nodes. These descriptive anatomic pathways correspond closely with actual patterns of postresection locoregional failure, observed most often in the ipsilateral para-aortic/paracaval and renal hilar regions, without contralateral extension. Based on these findings, Gaujoux and Brennan proposed a systematic dissection involving celiac, renal hilum, para-aortic, and/or paracaval lymph nodes ipsilateral to the tumor extending from the aortic hiatus to the renal vein. Reibetanz and colleagues proposed a similar, but laterality-specific, approach: for right-sided ACC, boundaries for lymphadenectomy are the lower edge of liver (upper), border of the IVC (left lateral), and renal pedicle (lower). For left-sided ACC, boundaries are the diaphragmatic crus (upper), border of aorta (right lateral), and renal pedicle (lower).

**IS THERE EVIDENCE TO SUPPORT MINIMALLY INVASIVE RESECTION FOR KNOWN OR SUSPECTED MALIGNANCY?**

Laparoscopic adrenalectomy (LA) has emerged as the standard of care for management of functioning and nonfunctioning tumors when suspicion for malignancy is low. For such indications, LA is associated with reduced postoperative pain, shorter hospital stay, and lower overall costs. For known or suspected adrenal malignancy, however, open adrenalectomy (OA) has been favored; advocates of this approach purport a decreased risk of capsule breach or tumor fragmentation. The growing expertise with laparoscopy for non-ACC histologies has led to the increased application of minimally invasive approaches in ACC. Early reports, mostly single cases or small series, revealed prohibitive rates of peritoneal and port-site carcinomatosis, local recurrence, R1/R2 resections, tumor fragmentation, and capsule rupture after LA.

More recent evidence from high-volume centers, particularly in the United States, recapitulate the dismal outcomes following LA. In a series of 160 patients (OA, 154; LA, 6) from the MD Anderson Cancer Center, local recurrence and peritoneal carcinomatosis were components of initial failure in 100% and 83% of patients undergoing LA, compared with 35% and 8% undergoing OA, respectively \( (P = .0001) \). In a contemporary report from the same institution including 302 patients (OA, 256; LA, 46) with ENSAT stage I–III ACC, an increased risk of multifocal peritoneal carcinomatosis was redemonstrated in the LA cohort compared with patients undergoing OA at either the referring or index institution. Moreover, the use of laparoscopy was independently associated with worse recurrence-free and overall survival (both \( P < .0001 \)) on multivariable analysis.

Although these studies have been criticized for including ACCs resected laparoscopically at lower-volume referring hospitals, which may have negatively skewed the observed oncologic results, it seems that outcomes following LA are consistently poor regardless of hospital volume. Reporting on their cumulative experience with 156 patients (OA, 110; LA, 46) with ENSAT stage I–III ACC between 2003 and 2008, the high-volume University of Michigan group demonstrated a significantly shorter time to locoregional and peritoneal recurrence \( (P = .002) \), higher rates of margin-positivity or intraoperative tumor spillage (LA, 30% vs 16%; \( P = .04 \)), and decreased overall survival \( (P = .002) \) following laparoscopic resection.

Mir and colleagues from the Cleveland Clinic reported on 44 patients with ACC (OA, 26; LA, 18); patients selected for LA had smaller tumors and less advanced stage. After controlling for stage by Cox regression, OA was associated with lower risk of recurrence (HR, 0.4; \( P = .099 \)) and
improved overall survival (HR, 0.5; \(P = .122\)) compared with LA, although these differences did not achieve significance owing to statistical underpowering. Concerns regarding the widespread adoption of LA for ACC are reflected in a position statement from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES): “For ACC, the best determinant of patient outcomes is an appropriate oncologic resection that includes en bloc resection of any contiguous involved structures and regional lymphadenectomy. Thus, an open approach to resection may be best.”

Oncologic outcomes following LA for ACC from select European centers compare favorably with those reported by most US institutions. In a report of 152 (OA, 117; LA, 35) patients with ENSAT stage I–III disease from the German ACC registry, recurrence-free (HR, 0.91; \(P = .69\)) and disease-specific (HR, 0.98; \(P = .92\)) survival did not differ between OA and LA cohorts in a risk-adjusted model adjusting for stage, tumor size, adjuvant therapy, and presence of glucocorticoid excess. In a multi-institution Italian study of 156 patients (OA, 126; LA, 30) with node-negative (ie, stage I/II) disease, unadjusted 5-year disease-free \((P = .12)\) and overall \((P = .2)\) survival were equivalent between OA and LA cohorts. A French single-institution report examining 34 patients with stage I/II ACC and tumor size less than 10 cm (OA, 21; LA, 13) demonstrated similar unadjusted disease-specific \((P = .65)\) and disease-free \((P = .96)\) survival between the 2 approaches. The latter study emphasized the importance of careful patient selection when considering LA for known/suspected ACC, a position echoed by the European Society of Endocrine Surgeons (ESES): “Laparoscopic resection of ACC...may be performed for pre-and intraoperative stage I–II ACC and tumors with diameter <10 cm.”

Given these conflicting data, the oncologic advantages of open resection still seem to outweigh the short-term benefits of a minimally invasive approach for suspected ACC, a position that is supported by consensus guidelines from the National Comprehensive Cancer Network. It is possible, however, that experienced laparoscopists may opt for an initial laparoscopic approach in selected patients presenting with smaller well-circumscribed lesions that are diagnostically ambiguous. In such cases, meticulous attention to surgical technique is paramount, and a low threshold should be maintained for open conversion if intraoperative findings are concerning for malignancy.

**IS THERE A ROLE FOR AN AGGRESSIVE SURGICAL APPROACH IN LOCALLY RECURRENT OR METASTATIC DISEASE?**

Distant metastasis at initial presentation is common in ACC, with 21% to 39% of patients presenting with single-site or multifocal metastatic disease. Moreover, up to 80% of patients with ACC present with local or distant recurrence following initial radical resection. These patients have a similarly poor prognosis; 5-year disease-specific survival is typically less than 15%. Despite these statistics, few data exist on the optimal management of patients with locally recurrent or metastatic disease. The uncertain benefit of salvage chemotherapy and hormonal therapy, poor tolerability of these regimens (particularly mitotane plus etoposide, doxorubicin and cisplatin [EDP-M]), short-term efficacy of resection in controlling symptoms of hormone excess, and improvements in perioperative care support an aggressive surgical approach in selected patients.

Outcomes in patients with ENSAT stage IV ACC receiving the best available chemotherapeutic and hormonal agents as sole therapy remain dismal; based on FIRM-ACT (First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment) trial results, EDP-M treatment yielded response rates of 23%
and median survival around 14 months.\textsuperscript{73} Although data regarding the role of aggressive surgery in patients with synchronous metastasis are scarce, it is increasingly applied when complete resection of primary tumor and all metastases is technically feasible.\textsuperscript{7,71,74} In a retrospective analysis of 27 patients with synchronous single- or multisite metastasis involving lung, liver, and brain, R0 resection, achieved in 11 (40.7\%), was associated with improvements in median (28.6 vs 13.0 months), 1-year (69.9\% vs 53.0\%), and 2-year (46.9\% vs 22.1\%, all $P = .02$) overall survival compared with R2 resections. Furthermore, unadjusted analysis demonstrated that receipt of neoadjuvant EDP-M was associated with a trend toward improved survival (5-year, 41.7\% vs 8.9\%; $P = .1$) compared with surgery alone, although adjuvant mitotane with or without cytotoxic chemotherapy seemed to decrease recurrence in patients selected for a surgery-first approach (see section “What are the current and emerging options for multimodality management of adrenocortical carcinoma?”).\textsuperscript{74}

These data underscore the importance of a multimodality approach, incorporating aggressive surgery with the goal of complete resection. Other studies, although heterogeneous in their design owing to inclusion of both synchronously metastatic patients and those with metachronous metastasis following initial resection, suggest that complete resection may be of benefit in the former group.\textsuperscript{25,69,75}

The role of aggressive reoperation for metachronous distant metastasis or local recurrence following initial radical resection is better defined. In a single-institution report of 47 patients undergoing reoperation for distant metastasis ($n = 21$) or local recurrence ($n = 11$), completeness of second resection (R0, $74$ vs R2, 16 months; $P < .001$) but not pattern of recurrence (distant vs local; $P = .27$) was critically important for long-term survival. Complete repeat resection was more readily accomplished for isolated/oligometastatic distant lesions compared with bulky local recurrences.\textsuperscript{25} In a multi-institution Italian cohort of 52 patients with recurrent disease, mean survival (15.9 vs 3.2 months) and 5-year actuarial survival (49.7\% vs 8.3\%, $P = .00006$) were significantly higher in patients who underwent reoperation ($n = 20$, 38.5\%) compared with patients who did not undergo resection.\textsuperscript{40} In a heterogeneous single-institution cohort of 28 patients undergoing hepatectomy for either synchronous ($n = 11$) or metachronous ($n = 17$) liver metastasis, all patients had recurrence either locoregionally or in the liver and/or another distant site; of these, recurrence was treated surgically in 11 (39.3\%) patients. Surgical treatment of recurrence was an independent prognosticator of overall survival after adjusting for tumor laterality, hormone secretion, and extent of initial hepatectomy.\textsuperscript{69} Of 154 patients from the German ACC registry with recurrent disease following initial radical resection, 42 (27\%), 57 (37\%), and 55 (36\%) patients incurred local recurrence alone, metastatic disease alone, and both local recurrence and distant metastasis, respectively; lung and liver were the most common sites of metastasis. In a Cox proportional hazards model adjusting for age, sex, number of affected sites, and receipt of additional therapy, R0 resection ($n = 33$) was associated with improved progression-free and overall survival.\textsuperscript{5}

In the latter study, multivariable analysis also identified time to first recurrence (ie, disease-free interval [DFI]) greater than 12 months as an independent prognosticator of survival; patients ($n = 22$) with DFI greater than 12 months and R0 resection demonstrated a median progression-free and overall survival of 24 and greater than 60 months, respectively.\textsuperscript{5} In parallel with these findings, Datrice and colleagues\textsuperscript{75} reported 116 metastasectomies performed in 57 patients at the National Institutes of Health; on univariate analysis, DFI greater than 12 months was associated with longer survival (6.6 vs 1.7 years, $P = .015$) than shorter DFI. In a separate study from the same institution describing 60 pulmonary metastasectomies in 26 patients, median overall survival was significantly longer in patients with time to progression/recurrence greater than 17 months.
Based on the available evidence, the authors recommend that, in addition to nuanced clinical judgment regarding the technical feasibility of metastasectomy (ie, ability to perform an R0 resection), aggressive surgery should be restricted to selected patients with DFI of at least 6 months or greater (ie, favorable tumor biology).

Two additional considerations in the surgical management of recurrent/metastatic ACC deserve mention. First, nonresectional ablative modalities (eg, radiofrequency ablation and/or transarterial chemoembolization) may be valuable adjuncts to surgical resection in selected cases. Second, in recurrent/metastatic ACC cases in which complete resection is not technically possible, cytoreductive debulking may be considered for symptom palliation when hormone excess is refractory to medical management.

WHAT ARE THE CURRENT AND EMERGING OPTIONS FOR MULTIMODALITY MANAGEMENT OF ADRENOCORTICAL CARCINOMA?

The aggressive behavior of ACC underscore the need for effective adjuvant or neoadjuvant regimens. Probably owing to the low incidence of ACC, level I evidence is lacking. The agent supported by the largest body of available evidence, and the only drug approved by the US Food and Drug Administration for ACC, is mitotane, a potent adrenal corticolytic. In a multinational retrospective analysis of 177 patients with stage I–III ACC who underwent radical surgery (1985–2005), Terzolo and colleagues compared 47 Italian patients who received adjuvant mitotane with 55 Italian and 75 German patients who did not; receipt of adjuvant mitotane was associated with improved disease-free survival (42 months vs 10 months for Italian control group and vs 25 months for German control group), after adjusting for age, sex, tumor stage, and treatment group in a multivariable analysis. Despite skepticism regarding benefit, poor tolerability, challenging pharmacokinetics (ie, narrow therapeutic window, need to closely monitor drug levels), modest tumor response rates (ie, 10%–30% in most patients), and mixed results with adjuvant use in other uncontrolled studies, an international panel recommended that adjuvant mitotane be offered to patients with R1/Rx resection and Ki67 greater than or equal to 10%, but not considered mandatory in groups at presumably low/moderate risk of relapse (eg, stage I–III ACC undergoing R0 resection, Ki67 <10%). The prospective multinational ADIUVO (Efficacy of Adjuvant Mitotane Treatment) trial, which randomizes patients to adjuvant mitotane versus watchful waiting, will assess the benefit of adjuvant mitotane in low- and moderate-risk patients.

Data on cytotoxic chemotherapeutic agents of benefit in ACC are scarce, and regimens demonstrating benefit in the advanced/metastatic setting are typically applied in the adjuvant setting. The FIRM-ACT trial established EDP-M as the first-line treatment in metastatic ACC compared with mitotane and streptozosin; tumor response rates \( P < .001 \) and progression-free survival \( P < .001 \), but not overall survival \( P = .07 \), were significantly improved with EDP-M. Based on the available data, platinum-containing adjuvant regimens, in combination with mitotane, are typically favored in patients at high risk of recurrence who have undergone resection. Cisplatin-mitotane may be a reasonable alternative in patients unfit for EDP-M. Cytotoxic chemotherapy without mitotane is largely ineffective. In parallel with developments in other aggressive solid tumors (eg, pancreatic and gastric cancers), there is increasing interest in applying chemotherapy/hormonal therapy in the neoadjuvant setting in ACC, particularly for borderline resectable patients. Preliminary retrospective evidence suggests a potential benefit in select patient subgroups with such an approach.

The modest efficacy and poor tolerability of available adjuvant regimens, as well as growing understanding of the molecular underpinnings of adrenal tumorigenesis, have generated interest in directly targeting dysregulated signaling in ACC with...
molecular-based therapies. The application of tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor–induced downstream signaling (eg, erlotinib, sunitinib) has yielded variable results in advanced ACC.95,96 Another novel target in ACC is the IGF-1 receptor (IGF1R); anti-IGF1R monoclonal antibodies (ie, figitumab, cixutumumab) and anti-IGF1R TKI OSI-906 (linsitinib) have been used in chemorefractory metastatic ACC with encouraging results.97,98 The phase 3 placebo-controlled GALACCTIC trial, evaluating the survival impact of OSI-906 in patients with locally advanced/metastatic ACC, is currently recruiting patients (NCT00924989). It is possible, although unproven, that such targeted therapies may mitigate recurrence if applied in the perioperative or adjuvant settings.

Adjuvant radiotherapy in ACC, previously considered a radioresistant tumor, may be selectively considered in patients with a high risk of local recurrence (ie, R1/Rx resection, ENSAT stage III disease, tumors >8 cm, microvascular invasion, and Ki67 ≥10%),7,48 although these recommendations are largely based on uncontrolled retrospective data.99–101 Conversely, the role of radiotherapy in the palliative setting is better defined, particularly for symptomatic bone or cerebral metastasis or in unresectable intra-abdominal recurrences that cause vascular or intestinal obstruction.48

PROPOSED APPROACH TO THE MULTIMODAL MANAGEMENT OF LOCALIZED ADRENOCORTICAL CARCINOMA

An algorithm for multimodal management of localized ACC is proposed (Fig. 2).

Fig. 2. Proposed multimodal management of localized ACC amenable to radical resection. a Consider neoadjuvant combination therapy (mitotane ± EDP chemotherapy) if borderline resectable; b high risk: Ki67 index greater than or equal to 10% (EDP, etoposide, doxorubicin, cisplatin; NED: no evidence of disease).
SUMMARY

Preoperative assessment of the patient with suspected ACC should include biochemical workup to characterize functionality and high-resolution imaging to determine extent of disease. Biopsy is rarely indicated. Prognosis is determined by ENSAT/AJCC tumor stage and completeness of resection. Gene expression profiling is emerging as a powerful predictor of prognosis but is not widely available. Complete resection with negative margins is the goal of surgical management and may require multivisceral resection, tumor thrombectomy, or vascular resection with or without reconstruction. Minimally invasive approaches have been advocated by select centers with expertise and have been extensively applied to the resection of benign or ambiguous lesions; notwithstanding, likely malignant and locally advanced lesions in particular are most safely managed with an open approach. Resection of adjacent organs not obviously involved by tumor is not indicated. Regional lymphadenectomy may provide valuable staging information or be associated with a disease-free or overall survival advantage and is probably underused. Recurrence is associated with poor prognosis; however, selected patients with limited or symptomatic disease may benefit from surgery. Data for specific multimodal approaches are limited; however, a role for adjuvant mitotane after resection of high-risk lesions is widely accepted.

REFERENCES


