

Practical Considerations in the Evaluation and Management of Adrenocortical Cancer

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Adrenocortical cancer (ACC) is a rare, challenging disease with a broad range of clinical presentations. Often presenting in an advanced stage with a large, locally invasive primary tumor or with Cushing's syndrome, it requires a multidisciplinary approach to treatment. We discuss controversies in the evaluation and management of ACC. We conclude that the role of ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) remains unclear and that it should be employed sparingly. Biopsies should be performed only when metastatic disease is present and a primary tumor has not been clearly established. Care should be taken in using the Weiss criteria to make decisions regarding prognosis. Surgery is the preferred intervention initially and at the time of recurrence, and every effort should be made to attempt a surgical resection. The latter should be an open resection; laparoscopic resection should not be performed if there is a high suspicion of ACC. The use of mitotane in patients without evidence of disease remains controversial. Systemic chemotherapy is effective in patients with widely metastatic disease or as an adjunct to a surgical intervention and should focus on regimens that have been shown to effect responses; "novel targeted therapies" should not be employed as first-line treatment. Radiofrequency ablation (RFA) and cryoablation can be very helpful but are still under evaluation; embolization with or without chemotherapy may be used as a surgical adjunct. The role of radiation remains to be defined. Finally, physicians caring for these patients need to recognize that Cushing's disease is a debilitating problem that should be managed aggressively; expecting chemotherapy to solve this complication is not appropriate.

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Adrenocortical carcinoma (ACC) is a rare tumor with an incidence of 1.5 to 2 per million per year. It has a very poor prognosis with an overall 5-year mortality rate of 75% to 90% and an average survival from the time of diagnosis of 14.5 months. Signs and symptoms due to excess hormonal secretion are seen in a large fraction of patients, further contributing to the morbidity associated with this disease. The reader is referred to several recent reviews for a fuller understanding.¹⁻⁵

Although a rare disease, ACC presents many diagnostic and management challenges that involve pathologists, endocrinologists, surgeons, and oncologists. This contribution will address some of these challenges, providing the reader with the necessary back-

ground together with opinions based on the available literature and extensive personal experience in the management of these patients.

EVALUATION AND WORK-UP

The evaluation of a patient presenting for the first time with an adrenal mass that may be ACC should include a history and physical examination, together with blood and urine tests to ascertain whether the tumor is functional. Imaging studies are an important adjunct to define the extent of disease as accurately as possible. Because surgical resection remains the only curative option for ACC, the approach from the outset should be to determine whether the patient's presentation is one that warrants a surgical intervention.

Both computed tomography (CT) and magnetic resonance imaging (MRI) can help to discriminate benign adenomas from malignant lesions and should be used to assess patients suspected of having ACC. On CT scans ACCs are typically inhomogeneous and because of their lower lipid content usually have higher density values; on MRI they are usually iso-intense with liver on T1 images, with intermediate to high intensity on T2

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images.⁶⁻⁸ However, MRI is superior in assessing the extent of vascular invasion—especially inferior vena cava (IVC) involvement that frequently complicates right adrenal tumors—and should be obtained prior to surgery to determine the extent of IVC involvement, if any.⁹ MRI is also preferable for assessing liver metastases prior to undertaking a surgical resection, or if liver metastases are to be followed in assessing response to therapy, in which case a baseline MRI should be obtained prior to starting therapy. Unlike MRI and CT scans, whose value is widely accepted, the utility of ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) in screening and routine follow-up remains to be established.¹⁰⁻¹² While studies have shown FDG-PET can visualize most ACCs and help to discriminate benign from malignant adrenal masses, unfortunately small lesions are a source of false-negative results and benign adenomas can present as positive lesions.¹¹ In discriminating adenoma from carcinoma, some investigators have advocated comparing the intensity of the adrenal lesion to that of liver, arguing that adrenal mass activity visibly less than liver is more specific for adenoma, whereas that visibly greater than liver is more specific for malignancy; however, this supposition must be validated further.^{13,14} Advocates of using FDG-PET argue that the sensitivities for the detection of individual lesions and the diagnosis of metastatic sites are comparable if not better for PET/CT compared to conventional imaging techniques,¹² but, in fact, lesions detected by more “conventional imaging” are often missed by FDG-PET, precluding its use as the only modality. Furthermore, assertions that many local relapses are seen “only with PET/CT” ignores that these relapses would have been eventually identified by conventional imaging techniques and does not address whether surgery performed a few weeks to a few months earlier can improve survival—a possibility that seems highly unlikely even if the diagnosis is indeed made earlier by FDG-PET. This also ignores the all too frequent problem of nonspecific uptake in the surgical bed that requires follow-up to clarify whether the activity seen is recurrent disease or postsurgical inflammation. We would finally note that while FDG-PET might help discriminate a benign adenoma from a malignant tumor, it could not differentiate ACC from other tumors with high metabolic activities.¹⁵ Thus, like all other imaging studies, FDG-PET is not infallible and can only be considered at best an ancillary procedure that cannot be recommended as routine in the evaluation of patients with ACC, and it should not be used serially to assess the efficacy of a chemotherapy regimen given the variability that can occur with standard uptake values (SUVs). However, although FDG-PET should not be used routinely, it may assist in the presurgical evaluation of a patient, especially if the finding of occult disease might alter the surgical approach or prompt a nonsurgical strategy.¹⁶

THE ROLE OF BIOPSY

In a patient presenting with an adrenal mass, careful deliberation is warranted in deciding whether a biopsy should be performed. The risk of seeding tumor—although not quantified—and the difficulty differentiating benign from malignant in a small biopsy sample, must be considered in making the decision.^{17,18} In a patient with symptoms referable to excess hormone production, manifested either as frank Cushing’s syndrome or subclinical hormone excess measured in a 24-hour urine collection, the diagnosis of ACC is usually not in doubt and the need for a diagnostic biopsy is obviated. But in a patient whose presentation has been that of pain, or of a mass found incidentally on an imaging scan, the clinical presentation should guide the decision. If the search for a primary tumor that might be responsible for an adrenal metastasis fails to identify a source and the physician is faced with an isolated adrenal mass, then surgical resection is indicated as both a diagnostic and therapeutic procedure; a diagnostic biopsy should not be undertaken in a patient with an isolated adrenal mass without evidence of metastases. However, if widespread metastases argue against surgical resection or if disease elsewhere suggests a primary location other than adrenal, a diagnostic procedure is indicated. In a patient with metastatic disease an excisional biopsy is preferred if one can be performed.

PATHOLOGIC ASSESSMENT

Distinguishing a small, 4- to 6-cm ACC without local spread or distant metastases from a benign adenoma can be challenging. To assist in the differential, several multi-parametric approaches have been proposed for establishing malignancy. Among these, the “Weiss criteria,” first proposed in 1984, is most widely used.¹⁹⁻²³ It is based on nine histopathologic properties of adrenocortical tumors that were established unequivocally as malignant either because they metastasized or recurred locally. According to Weiss, a combination of these “nine criteria was most useful in distinguishing malignant from benign tumors”: (1) nuclear grade III/IV; (2) mitotic rate greater than 5 per 50 high-power fields (HPFs); (3) atypical mitoses; (4) tumors with 25% or less clear cells; (5) diffuse architecture; (6) microscopic necrosis; (7) venous invasion; (8) sinusoidal invasion; and (9) capsular invasion. Weiss originally reported finding no metastases or recurrences in 24 tumors with 0-2 criteria compared with metastases or recurrences in 18/19 with ≥ 4 criteria, and suggested the presence of four criteria as a threshold for malignancy; this threshold was subsequently lowered to ≥ 3 of the nine histopathologic criteria.

While the Weiss criteria can help discriminate a small adenoma from a small carcinoma, their value in

larger tumors that may have spread locally or even metastasized to a distant site is not established. Although the nine properties often cluster, the issue of whether the presence of a greater number of criteria is associated with a worse prognosis is not clear. If one compares small adenomas and large ACCs, as was recently reported, there will be great differences in the Weiss scores of these presentations.²⁴ However, this was not the use envisioned by Weiss when he first developed the criteria. Weiss and colleagues addressed this in a subsequent study where they set out to assess pathologic prognostic factors that would be helpful in distinguishing low-grade versus high-grade ACCs.²⁰ Remarkably, among 42 patients with a diagnosis of ACC, only one of 11 pathologic parameters—mitotic rate—had a strong statistical association with outcome. Specifically, the median survival of the 21 patients whose carcinomas had greater than 20 mitoses per 50 HPFs was 14 months, compared to a median survival of 58 months for the 21 patients whose carcinomas had ≤ 20 mitoses per 50 HPF ($P < .02$). Other parameters, including some of those comprising the Weiss criteria such as the presence of atypical mitoses and capsular invasion as well as a tumor weight greater than 250 g and size greater than 10 cm, each showed a marginal statistical association with poor survival ($P < .06$). However, nuclear grade, presence of necrosis, venous or sinusoidal invasion, character of the tumor cell cytoplasm, and architectural pattern had no statistical power for predicting survival. The authors proposed that adrenal cortical carcinomas with greater than 20 mitoses be designated high grade, whereas tumors with ≤ 20 mitoses be designated low grade. Thus although clinically tumors with higher Weiss scores often behave more aggressively, the prognostic value of pathologic findings other than mitotic rate remain unconfirmed. That mitotic rate is important has been confirmed in a recent study that attempts to simplify histopathologic classification of ACCs.²⁵

MANAGEMENT OF ACC

In general terms, three options are available for the management of ACC: surgical resection, oral mitotane, and intravenous chemotherapy. However, many management issues remain unsolved, in part because of the rarity of the disease and the paucity of data together with the challenges presented by large retroperitoneal tumors that have often metastasized locally and to distant sites. We address these below, again providing relevant background and opinions based on the available information and our experience managing patients with ACC.

Surgical Resection

General Considerations— Preoperative Assessment

Because patients may not present with overt symptoms of hormonal excess, yet they have “subclinical” hormone production, it is important to assess hormonal status, especially if a surgical intervention is planned. The primary goal is to avoid adrenal insufficiency in the postoperative period by assessing the need for steroid replacement after removing a functioning tumor that suppressed corticotropin (ACTH) with involution of the contralateral adrenal.

Laparoscopic Versus Open Surgery—The Controversy

While an occasional patient can achieve a sustained remission from oral mitotane or a combination chemotherapy regimen, for the majority of patients with ACC the only proven curative option remains surgical resection. For a successful outcome, a multidisciplinary approach such as the one discussed below is required. As regards surgery, the goals are to have the procedure performed by an experienced surgeon and that the surgery will not have an unwanted outcome.

At the initial presentation, the increasing availability and use of laparoscopic surgery for this rare disease has generated controversy over the best surgical management: open or laparoscopic surgery. In our opinion, the answer is clear: patients with a suspected or known ACC should undergo an open procedure. A laparoscopic surgery should not be performed. While we would agree the literature for this has not yet been fully written, let us address the controversy as candidly as possible.

We would begin by noting that laparoscopic surgery for an adrenal incidentaloma is appropriate. But it is here the problem arises. A surgeon in the community is likely to see 10 to 100 or more benign incidentalomas for each ACC. Such surgeons become comfortable with laparoscopic adrenalectomies, recognize the ease with which they are performed and the uneventful postoperative recoveries but do not then discriminate a malignant ACC from a benign incidentaloma. To the surgeon in the community both the benign incidentaloma and an ACC present similar surgical challenges. Unfortunately, while incidentalomas do not seed the abdomen, an unacceptable fraction of ACCs resected laparoscopically—with an intraoperative tumor spill rate as high as 50%—even by an experienced laparoscopic surgeon, will seed the abdomen.²⁶ A surgeon who claims that seeding has never been a problem for one of his patients either has not performed enough laparoscopic procedures on patients with ACC or does not participate in their long-term follow-up. Peritoneal disease then becomes an intractable and incurable prob-

lem, and the resultant outcome is one of patient harm secondary to a laparoscopic procedure that was viewed initially by the surgeon as one that would bring benefit to the patient in terms of postoperative recovery time.

Brix et al have recently reported the surgical and oncologic outcome in 152 ACC patients comparing laparoscopic versus open adrenalectomy at the time of initial presentation.²⁷ These investigators concluded that, "For localised ACC with a diameter of ≤ 10 cm, laparoscopic adrenalectomy by an experienced surgeon is not inferior to open adrenalectomy with regard to oncologic outcome." This simplified conclusion obscures the nuances found in the data. The study describes the outcomes in individuals participating in a well-structured healthcare system where a patient with a rare disease such as ACC is likely to be referred to an experienced surgeon. While the report was confined to 152 patients with ACCs that were ≤ 10 cm in maximum diameter and were deemed potential laparoscopic candidates, surprisingly only 35 (23%) underwent a laparoscopic resection. Thus one can immediately see that extensive preselection occurred during the decision-making process. Indeed as the authors noted, "the frequency of stage III patients was higher in the [open adrenalectomy (OA)] group compared with the [laparoscopic adrenalectomy (LA)] group (32.5% *v* 11.4%; $P < .001$) because in the LA group all tumors were considered as stage I/II prior to surgery." Furthermore of the 35 patients in whom a laparoscopic resection was attempted the procedure was converted to an open laparotomy in one third ($n = 12$) leaving only 23 patients who underwent laparoscopic resection. This represents approximately 15% of patients with tumors ≤ 10 cm, and about 7% of all ACC patients evaluated during this period that did not have overt metastatic disease at presentation (other exclusions were 38 patients due to age < 16 years, 138 patients due to distant metastases, 160 patients due to tumor size > 10 cm, and 29 patients due to missing on the surgical procedure or follow-up). In the end, the only conclusion that can be drawn is that in a well-structured medical system such as the German system, where patients with a rare disease such as an ACC are referred to the care of a highly experienced surgeon, laparoscopic adrenalectomy may be an acceptable alternative for a small fraction of patients presenting with ACC, provided they present with a tumor that is less than 10 cm in diameter, and only after they have undergone extensive pre-treatment evaluation that excludes 77% as candidates for laparoscopic adrenalectomy. The applicability of these results to the general community is very limited to none, but unfortunately, as presented, risks the very real possibility that this will be more broadly interpreted as an endorsement of laparoscopic resection for a much larger fraction of ACC patients. Indeed in the United States this would mean that annually no more

than 35 patients with ACC would be potential candidates, and to think that "diverting" such patients from an open adrenalectomy to a laparoscopic procedure would in any way impact health care is not realistic.

The report by Brix et al notwithstanding, many feel that laparoscopic adrenalectomy should not be performed in a patient with known ACC.^{26,28} Complications of laparoscopic resection that have been reported include (1) a much higher likelihood of recognized or unrecognized intraoperative tumor spill with peritoneal seeding resulting in carcinomatosis even in the hands of an experienced surgeon; (2) positive margins; and (3) more rapid recurrence. Given our still limited systemic chemotherapy options, an earlier peritoneal recurrence not amenable to surgical resection is a serious adverse event that should be avoided. We would further note that even those who have reported comparable outcomes with laparoscopic surgery recognize that "*open surgery is still the recommended approach in ACC*" while noting that "in localized non-invasive ACC with a diameter less than 10 cm laparoscopic adrenalectomy by an expert surgeon is *probably* similarly effective and safe" (emphasis added).²⁹ Finally, a recent systematic review of laparoscopic surgery for cancer noted that "adrenocortical cancer and malignant pheochromocytomas are rare tumors with a poor prognosis, likely not well-suited to laparoscopic approaches" and concluded that "at this time, there are no prospective randomized series to guide or endorse the use of laparoscopic resection for adrenocortical carcinoma or malignant pheochromocytoma."³⁰

Mitotane

The discussion regarding attempts to classify ACCs and predict their biologic behavior has relevance in 2010 primarily to the use of mitotane. While knowledge of the aggressiveness of the patient's ACC and especially of the likelihood of a recurrence could help guide a decision for or against metastasectomy or more radical surgery, it is in deciding whether or not to use mitotane that such information would be most valuable—although unfortunately, at present, it is not conclusive. And although the available data cannot be considered conclusive, they suggest that mitotane given in an adjuvant manner, albeit indefinitely, can at a minimum delay and possibly prevent a recurrence of disease.³¹ While mitotane is well tolerated by a fraction of patients, in fact the majority of patients find mitotane a difficult therapy that markedly impacts the quality of their lives. Because not all patients who undergo surgical resection suffer a relapse, a therapeutic approach that administers mitotane to all patients after an initial resection will have a negative impact on the lives of the 20% to 35% of patients who have been cured by the surgical intervention, without any possible benefit. This problem alone then can only begin to be solved by

the identification of an accurate predictor of recurrence. While a physician can feel comfortable recommending mitotane indefinitely to a patient who presents with a 14-cm primary tumor and undergoes a resection with very small margins and has evidence on histopathology of extensive necrosis, lymphatic, vascular, and capsular invasion and a high mitotic rate, such would not be the case for a well-encapsulated 6-cm ACC without evidence of spread and three Weiss criteria. We would thus argue that as regards mitotane early in the disease, the lack of convincing data, and the difficulty administering most doses, argues for its use only if the tumor cannot be removed surgically, or as adjuvant therapy only if there is a high likelihood of recurrence.^{4,32}

SYSTEMIC CHEMOTHERAPY

As might be expected for a rare disease, the therapy of ACC suffers from a scientific database that is very limited and that might be characterized as a collection of anecdotes, albeit some larger than others. Nowhere is this more apparent than in the chemotherapy of ACC. The mitotane controversy has been addressed above and one might argue the choice of what chemotherapy is best is also a “work in progress.” In general terms when assessing chemotherapeutic efficacy one can look at response rate and progression-free survival as two inter-related elements with overall survival as a different endpoint. In the case of ACC, assessment of response rate has been the principal mode of evaluation.

Two therapeutic regimens have emerged as viable options for ACC both using mitotane with either streptozocin alone, or in combination with etoposide, doxorubicin, and cisplatin (EDP).³³⁻³⁶ These two regimens have been recently evaluated in the international FIRM-ACT trial (First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment) and by 2011 there should emerge data that begin to allow us to compare their efficacy. The data in support of either of these regimens are limited, although physicians who treat patients with ACC can attest to their ability to shrink tumor at all sites. Streptozocin has been reported to have activity both in the adjuvant setting as well as in metastatic disease, although the number of patients treated and reported remains very small.^{33,34} The EDP combination has been the subject of several reports by the same group of investigators.^{35,36} Although clearly active, one must concede that the efficacy of EDP versus a simpler regimen has not been addressed. And given the toxicity associated with EDP administration, especially long-term, it should ideally be evaluated in a randomized trial against the combination of etoposide and cisplatin or even cisplatin alone. This suggestion is made since there is no compelling evidence that etoposide or

doxorubicin has single-agent activity against ACC and simpler regimens have shown comparable activity to the EDP combination. The latter include an earlier multi-institutional trial administering 75 to 100 mg/m² cisplatin with oral mitotane that achieved a response rate of 30%, and a study that reported a 33% response rate for a regimen consisting of 100 mg/m² cisplatin on day 1 plus 100 mg/m² etoposide on days 1 to 3 every 4 weeks.^{37,38} We would add that in our own experience single-agent cisplatin administered weekly is active in patients with ACC and is very well tolerated. Single-agent cisplatin also has the advantage that it can be used without dose adjustment in patients with alterations in liver function and in conjunction with full doses of ketoconazole in patients needing control of hormonal excess. A cisplatin dose of 40 mg/m² per week administered weekly without interruptions unless medically indicated for neutropenia or thrombocytopenia allows one to achieve a higher dose-intensity for cisplatin, the drug that many would agree has the most activity in ACC and which may have a steep dose-response curve, as evidenced by a much lower activity when only 50 mg/m² was administered with 100 mg/m² etoposide on days 1 to 3 every 21 days.³⁹ Finally, we would note that many patients with ACC have undergone nephrectomy and this often prompts physicians concerned about renal function to administer carboplatin instead of cisplatin. However, because experience in other cancers has found these two agents to not have similar activity profiles, pending published data with carboplatin, the drug of choice should remain cisplatin.

While ACC can be characterized as a “chemo-responsive” disease, with long-term disease-free intervals in some patients, it is clear that its sensitivity profile is limited.⁴⁰ Drugs that have been reported to have very little to no activity include 5-fluorouracil, capecitabine, gemcitabine, bevacizumab, erlotinib, and gefitinib.⁴¹⁻⁴³ Despite enthusiasm for “targeted therapies” in this difficult to treat disease, it is unlikely that ACC will fare much better than most other solid tumors have to date. Although it is hoped that some agents such as those targeting the insulin-like growth factor-1 (IGFR-1) axis may be shown to be effective in ACC, it is likely that such agents will need to be part of a combination regimen with, for example, cisplatin.⁴⁴ Consequently, patients with ACC should probably not receive a “novel targeted agent” before a trial of oral mitotane with either streptozocin or EDP. Indeed, since clinically these two regimens are not cross-resistant, they may be administered in succession if a response is not achieved with the first.

MANAGING PATIENTS WITH ACC—A MULTIDISCIPLINARY APPROACH

Managing patients with ACC requires a multidisciplinary approach involving medical, surgical, and radi-

ation oncologists, endocrinologists, and interventional radiologists. Both at presentation and at relapse the focus should be on whether a surgical intervention is possible, given this remains the most promising curative option for ACC. Unfortunately, despite aggressive surgery at the time of initial presentation, 70% to 85% of patients relapse locally or develop metastases, explaining a 5-year survival rate after complete resection of only 16% to 35% with survival less than 1 year in patients with incomplete resection.⁴⁵⁻⁴⁷ The latter argues strongly against a partial surgical resection since this can lead to intraoperative seeding and clearly has a poor outcome. However, much of the historical data did not envision an aggressive surgical follow-up, and it is this approach that we believe from our own experience will emerge as the preferred method of managing a “substantial fraction” of patients with ACC.⁴⁸ The substantial fraction of patients to be managed with repeated surgical intervention can be identified by their clinical presentation including the extent of local and metastatic disease, the pace of their tumor’s growth, the rapidity and pattern of recurrence, and the responsiveness of their tumors to chemotherapy. For example, a local recurrence in the surgical field is common following an optimal initial or subsequent resection and serious consideration should be given to a re-operation, especially if sufficient time—arbitrarily defined as 6 months to a year—has elapsed since the prior operation. However, patients whose disease recurs rapidly after extensive surgery or who develop widespread metastases should not be considered for a repeat surgical resection but should first undergo a trial of chemotherapy. The latter is often used as an “adjuvant or neoadjuvant” modality together with surgery. Given the rarity of achieving a long-lasting complete response with chemotherapy, the role of chemotherapy is to address metastatic disease, for example, in the lungs, and as a means of improving the outcome of a surgical resection by shrinking a tumor mass and possibly helping sterilize microscopic disease. Although we believe repeat surgery may improve survival, we recognize the extent of benefit is difficult to discern from published data since these are nonrandomized comparisons that likely encumber “no surgery” cohorts with patients with more aggressive disease presentations not amenable to re-operation.⁴⁹ However, we also believe the literature will eventually validate this approach.

Given the value of surgical intervention as a therapeutic modality, it is not surprising that radiofrequency ablation (RFA) or cryoablation have emerged as options for managing patients with ACC.⁵⁰ Either as an adjunct to surgery or as a modality to eradicate recurrences, both of these minimally invasive procedures offer promise. The decision paradigm for when to perform RFA or cryoablation should be the same as for a surgical intervention: RFA and cryoablation should be viewed

as surgical interventions, albeit less invasive. Thus, for example, just as a partial surgical resection should never be performed, an RFA or cryoablation that will not sterilize the site of tumor also should not be embarked upon. Also important in managing patients with ACC is embolization, either bland or with chemotherapy-loaded beads. While embolization is unlikely to sterilize a tumor site, it can be used in conjunction with surgery or with RFA or cryoablation as an intervention to reduce tumor size or ease a subsequent surgical procedure. We would note here that the role, if any, of administering radiation to the surgical field is not clear. Although initial studies reported a lack of benefit with adjuvant radiation, later studies possibly using better techniques claim high response rates with little toxicity.⁵¹⁻⁵³ However, we believe postoperative radiation should only rarely be administered following initial surgery and should be reserved for a select group after a second or subsequent re-operation pending clear documentation of benefit in a prospective study since such treatment may make a subsequent operation technically more difficult. The use of radiation therapy as a single-modality therapy without surgery cannot be supported.

Finally, it is important that physicians treating patients with ACC recognize that uncontrolled hormone production is a malignant disease with severe consequences requiring immediate and aggressive management.⁴ All too often medical oncologists look to chemotherapy to solve the problem of hormonal excess. However, this is a flawed strategy since chemotherapy will benefit only a minority of patients—meaning that a majority will be debilitated by the continued and increasing hormonal excess. Consequently, steroidogenesis inhibitors, including mitotane, ketoconazole, metyrapone, and etomidate, should be used singly or in combination with chemotherapy. Diligent management is required with frequent upward adjustments in doses, especially in patients with tumors that are refractory to chemotherapy and continue to grow.

CONCLUSION

Because surgical resection remains the principal curative option for ACC, the approach from the outset should be to determine whether the patient’s initial or subsequent presentation is one that can be managed surgically. If the answer is yes, every effort should be made to accomplish this. Chemotherapy, RFA, cryoablation, embolization, and radiation therapy are valuable adjuncts. Future efforts should be directed at improving chemotherapy options and conducting the necessary studies to validate current treatment paradigms with prospective, randomized clinical trials, thus replacing our largely anecdotal or retrospective database.

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