Adrenocortical Carcinoma: Past, Present, and Future

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INTRODUCTION

Adrenocortical carcinoma (ACC) remains a rare endocrine malignancy with an annual incidence of 0.5–2 per million people [1,2]. In spite of the stable prevalence at autopsy of adrenal tumors at 2.3% [3], the annual volume of adrenalectomies has increased 66% in the United States from 3,241 in 1998 to 5,323 in 2006 [4]. As there is no significant increase in malignant disease, it is concerning that this increase is associated with a concomitant rise in postoperative complications from 5.9 to 8.1% during the same time period.

In the last 20 years, there have been advances in the molecular basis of ACC. A clear understanding of the pathogenesis remains elusive, and there has been little improvement in survival. Systemic therapy, both adjuvant and palliative, remains unsatisfactory.

We provide a current overview of ACC and introduce potential avenues for advance in understanding of tumor biology and management.

DEMOGRAPHICS

Age distribution is bimodal with a peak <5 years of age and a second peak during the fourth to fifth decades (Fig. 1) [5–8]. In adults, the mean age of diagnosis is 45 years [9]. Compared to the incidence of pediatric ACC worldwide, the incidence of ACC is 10–15 times higher in children in southern Brazil, which is related to an inherited germline p53 mutation [10,11].

ACC affects women more commonly than men with a ratio of 1.5:1 [12–15]. Females with ACC are more likely to have functional tumors. Men with ACC tend to have functional tumors before the age of 20 years and nonfunctional tumors after the age of 40 years [1,7,16].

PATHOGENESIS

While ACC most commonly arises sporadically, it has been associated with a number of familial tumor syndromes, including multiple endocrine neoplasia type 1 (MEN-1; mutation of the MEN1 tumor suppressor at 11q13), Li-Fraumeni syndrome (p53 mutation on 17p13), Beckwith-Wiedemann syndrome (alterations of gene clusters on 11p15.5 and 15q11–13), and Carney complex (mutation of PRKAR1A gene at 17q23–24 or mutations at 2p16) [17].

In sporadic cases, the pathogenesis is not understood. Whether ACC develops de novo or develops from pre-existing hyperplastic or adenomatous nodules is not known. Evaluation of genetic alterations has identified multiple affected chromosomal regions, some of which overlap with mutations associated with named familial syndromes. Genome-wide screens for chromosomal alterations include microsatellite analysis and comparative genomic hybridization (CGH). Studies of the former have demonstrated that loss of heterozygosity (LOH) or allelic imbalances at 2p16, 11q13, and 17p13 are found in ≥85% of tumors and are highly specific for malignant tumors. Studies using CGH have demonstrated that up to 62% of ACC cases exhibit losses on chromosomes 1p, 2q, 11q, 17p, 22p, and 22q [17–20].

One of the most commonly identified mutations in ACC involves overexpression of the insulin-growth factor (IGF) gene [18,19,21,22]. IGF, which includes both IGF-1 and IGF-2, is involved in normal adrenal growth as well as adrenal tumorigenesis. The phosphoinositide-3 kinase (PI3K)-Akt and RAS-RAF-MAP kinase pathways are activated via IGF-1 and IGF-2 binding of the IGF1 receptor (IGF1R). Alterations of additional growth factors and growth factor receptors including epidermal growth factor (EGF), EGF-R, fibroblast growth factor (FGFR1 and FGFR2), transforming growth factor-α (TGFα), TGFβ1, vascular endothelial growth factor (VEGF), and VEGFR have also been implicated in the development of ACC [22].

CLASSIFICATION

ACC are classified as functional or nonfunctional. These tumors are inefficient in mature steroidogenesis, so to some degree, all ACC exhibit hormonal precursor excess. Clinical relevance is determined by the supraphysiologic hormone levels and symptoms. Commonly, symptoms are related to excess of corticosteroids, androgen, estrogen, and rarely, mineralocorticoids. It is important to search for the precursor steroid [especially dehydroepiandrosterone sulfate (DHEAS)] with serum and urine assays rather than to inappropriately classify a tumor as nonfunctional [1,7].

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ACC is staged on the basis of TNM. The first staging classification was published in 2004 and was based largely on the systems proposed by Macfarlane [23] and Sullivan et al. [24] (Table I) but is essentially classified into disease confined to the adrenal (Stage I or II) or extending beyond the gland (Stage III or IV) [25,26]. Pooled data from multiple institutions demonstrates that the majority of patients will present with regional or distant spread: 18% present with Stage III disease and 61% present with Stage IV disease. Only 21% present with either Stage I or II disease [25].

The purpose of the TNM staging is to provide prognostic oncologic outcome information for patients with cancer. However, due to the rarity of ACC, the prognostic value of the current system remains undefined. Revised classification systems have been proposed but have not been widely adopted [27].

CLINICAL PRESENTATION

Presenting signs and symptoms are the consequence of excess hormone or tumor mass. Approximately 60% of patients will present with functional tumors. Of these, corticosteroid excess is the most common with about 50% of patients exhibiting signs and symptoms of Cushing’s syndrome (Fig. 2). Easily recognizable and classic signs include truncal obesity, buffalo hump, rounded “moon” facies, stria, hypertension, as well as thinning of skin, osteoporosis, glucose intolerance, psychiatric disturbances, and renal calculi. Androgen-secreting ACC in women results in virilization with the associated hirsutism, deepening of the voice, breast atrophy, male pattern baldness, clitoral hypertrophy, oligomenorrhea, and altered libido. Estrogen-secreting ACC in men results in feminization with gynecomastia, breast tenderness, decreased libido, and testicular atrophy. ACC that exclusively produce aldosterone are rare with only about 2% demonstrating aldosterone excess as a predominant feature.

For those patients with nonfunctional tumors, signs and symptoms are generally related to mass effect. Ominous signs and symptoms include fever, anemia, pain, weight loss, and anorexia.

During evaluation of a patient, certain factors raise suspicion that an adrenal tumor is an ACC. These include: adrenal Cushing’s syndrome with a palpable or radiologically-confirmed mass, age < 20 years, lack of high dose dexamethasone suppression or increased urinary 17-ketosteroids or an adult with a palpable or radiologically confirmed abdominal mass with increased urinary 17-ketosteroids or 17-OH corticosteroids, feminization or virilization, or weight loss, anemia, or fever (Table II).

Most ACC present as large advanced masses. At MSKCC, the average tumor size at the time of presentation was 16 cm (range: 6–40 cm) and 1,190 g (range: 320–2600 g). As the incidence of incidentally discovered adrenal masses increases, it is possible that we will see a trend toward earlier stage at presentation. The majority of patients present with tumor extending beyond the adrenal. Metastatic spread is most common to the lungs (45%), liver (42%), or lymph nodes (24%) and less common to bone, pancreas, spleen, and diaphragm [1,16].

WORKUP AND DIAGNOSIS

Endocrine assessment prior to surgery is mandatory, and the pattern of secretion may provide insight into the malignant potential of the lesion. The most reliable screening test is the urinary free cortisol with a value >100 mg over 24 hr being abnormal [28]. An overnight suppression test, which involves administration of 1 mg of CORTISOL CARCINOMA: PAST, PRESENT, FUTURE

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Fig. 2. Signs and symptoms of patients with functional tumors.
dexamethasone at 11 pm and checking a serum cortisol level at 8 am on the following day, can confirm the diagnosis. Under normal circumstances, serum cortisol is suppressed to a level <5 mg/dl; suspect cortisol excess if cortisol levels are >10 mg/dl. DHEAS should be evaluated preoperatively because if elevated, may be used as a postoperative surveillance serum marker.

Radiologic studies can be employed to differentiate benign from malignant lesions and to determine resectability and relationships to surrounding structures. Size and appearance on radiologic imaging studies are considered the key to differentiating benign and malignant lesions. Size is the strongest predictor of malignancy and has long been used as a surrogate for adrenal malignancy. While only 2% of tumors ≤4 cm are found to be ACC, 6% of tumors 4.1–6 cm, and 25% of tumors >6 cm are found to be ACC [26,29]. According to the NIH consensus statement, patients with tumors >6 cm should be treated surgically.

As size alone cannot accurately discriminate between benign and malignant lesions, various radiologic techniques are employed [29,30]. Computerized tomography (CT) of ACC is the most useful study for determining resectability and relationships to adjacent structures. CT characteristics of ACC include heterogeneity, irregular borders, hemorrhage, central necrosis as well as central irregular enhancement and calcification. While these signs are nonspecific and can be found in association with other adrenal lesions (e.g., adenoma, pheochromocytomas, granulomatous disease, metastatic deposits), they are suggestive of ACC when found in the context of signs and symptoms. Advanced ACC may have local invasion and extend into lymph nodes, the adrenal and renal veins, the inferior vena cava (IVC), and surrounding structures.

Unenhanced density characteristics (Hounsfield units, HU) as well as intravenous contrast wash-out characteristics on delayed, contrast-enhanced CT images have become widely accepted for differentiating benign and malignant adrenal lesions. A meta-analysis of 10 studies concluded that the sensitivity and specificity of defining a lesion as benign using a threshold of <10 HU was 71 and 98%, respectively [31]. Furthermore, when applying absolute and relative washouts of 50 and 40%, retrospective analyses of patients with his- tologically confirmed masses and who underwent nonenhanced scans followed by 1- and 10-min delayed, intravenous contrast studies demonstrated that CT in this setting carries a sensitivity and specificity of 100% in differentiating adenomas from other lesions [14,32–34]. In conclusion, for lesions with >10 HU on unenhanced CT or a delayed washout of <50% with a delayed attenuation of >35 HU, ACC should be suspected [14].

Like CT, the use of magnetic resonance imaging (MRI) is based on the intracellular lipid differential between adenomatous and nonadenomatous lesions, with adenomas generally exhibiting a large amount of intracellular lipid. ACC, in general, are isointense to the liver on T1-weighted images and have intermediate-to-increased intensity of T2-weighted images. Consistent MRI ACC features include internal hemorrhage, central necrosis, and peripheral enhanc- ing nodules. While the optimum MRI technique is still debated, gad- olinium-enhanced MRI is associated with a sensitivity of 81–89% and a specificity of 92–99%. MRI also confers the additional advantage of assessing IVC involvement or invasion, a trait more commonly associated with right side tumors [7,14,35–38]. On the left side, the renal vein is more likely involved.

More recently, the role of [18F]fluorodeoxyglucose-position emis- sion tomography (FDG-PET) and PET/CT are being explored as potential means by which to differentiate benign and malignant adrenal tumors. Retrospective analysis of 175 masses demonstrated that PET misclassified 9 of 175 masses; this number was reduced to three with the addition of nonenhanced CT [39]. If contrast-washout characteri- zation was performed, sensitivity increased to 100% [40]. These studies were retrospective and were limited by sample size and a lack of histologic confirmation. Further validation studies are neces- sary to determine the role of FDG-PET and PET/CT in the differenti- ation of benign and malignant lesions. PET should be used in conjunction with other imaging techniques.

11C-metomidate-PET (MTO-PET) is an emerging adrenal imaging technique. Metomidate is an imidazole-based methyl ester and a poten- tient inhibitor of 11β-hydroxylase, an integral enzyme in the produc- tion of cortisol and aldosterone. As such, MTO-PET may be useful in the differentiation of lesions from cortical versus non-cortical ori- gins, but further studies are needed for validation [41–44].

There is limited data on the role of fine needle aspiration of inci- dental adrenal lesions in patients with no antecedent history of can- cer. CT-guided biopsy may be a useful in patients with a history of cancer (i.e., breast, kidney, lung), a heterogenous adrenal mass (HU >20), and no other signs of metastatic disease. There is a high level of accuracy (>90%) in histologic distinction of adenomas versus metastatic deposit. However, the sensitivity of cytologic evaluation in differentiating adenoma versus primary malignant adrenal lesion is less robust: 54–86% [45]. Due to the high false negative rate, a benign cytologic diagnosis does not rule out malignancy. Pheochromocytoma should be ruled out prior to adrenal biopsy.

PATHOLOGY

In the presence of metastatic disease or local invasion, the patho- logical diagnosis of ACC can be straightforward. Without these features, pathologic differentiation of benign versus malignant can be difficult. The Weiss criteria may be used to help make a post-resec- tion distinction. The system incorporates nine histologic features to help distinguish benign from malignant tumors: High mitotic rate (>5 per 50 high power fields (HPFs)), atypical mitoses, high nuclear grade (III or IV), low percentage of clear cells (<25%), necrosis, diffuse architecture of tumor, capsular invasion, sinusoidal invasion, and venous invasion. A score of 1 is given in the presence of a previously listed feature. A total score ≤2 is classified as an adeno- ma. A score >3 is suggestive of ACC. However, there is controversy surrounding the scoring system as a score of 2–3 is ambiguous and not all groups believe the system is reliable [15,19,26,46–49]. There is now increasing support for the use of adjunctive pathology to con- firm the diagnosis of ACC. Evaluation of markers including IGF-2 overexpression, allelic loss of 17p13, increased Ki-67, and differen- tial expression of genes (particularly those related to cell cycle) and microRNAs (miRNAs) may serve as molecular predictors of malig- nancy and provide valuable insight into oncologic outcome [50–52].

MANAGEMENT

Management of primary, recurrent, and metastatic ACC involves a multi-disciplinary approach.

Surgical Management—Primary Disease

Resection should be considered for tumors that demonstrate the following characteristics: tumor size >4 cm, presence of functional tumor, presence of radiologic characteristics including HU >20, washout <40–50% on delayed, contrast-enhanced CT, visual uptake on PET/CT, or MRI-confirmed internal hemorrhage, central necrosis, or peripheral enhancing nodules. As it is difficult to predict whether the contralateral adrenal gland will be atrophic and as earlier studies demonstrated that adrenal insufficiency is a major cause of postoperative morbidity and mortality [53], preoperative management should include careful attention to corticosteroid coverage and replacement. Some argue that postopera- tive steroid administration is unnecessary; however because virtually all tumors are biochemically active, we usually recommend postop- erative administration. We use hydrocortisone 100 mg intravenously.
on-call to the operating room and every 8 hr thereafter. Based on the degree of adrenal ablation, the daily dose of hydrocortisone is then tapered by 50–100 mg per day until a daily dose of 25–50 mg is attained. It can take up to 22 months for the benign adrenal to resume adequate steroid production, but the actual time for adequate response is shorter [1]. The simplest approach if there is suspicion of a nonfunctional, contralateral adrenal is to use an ACTH stimulus test. In the setting of bilateral adrenalectomy, the patient’s daily requirement will be approximately 37.5 mg of cortisone or the equivalent [54]. Fludrocortisone, a synthetic adrenocorticoid with potent mineralocorticoid effects, is given to patients after total adrenal ablation. The initial dosage is 0.1 mg three times per week and can be titrated according to serum electrolytes and weight gain, up to 0.1 mg/day. This is generally required after glucocorticoid doses have been titrated to maintenance levels.

When the decision is made to proceed with resection, one must select an operative approach. Surgery remains the only potentially curative treatment, and complete resection is critical. For lesions <10 cm, we recommend an anterior approach using a uni- or bilateral subcostal incision, which permits access to sites of potential invasion and metastatic spread. Routine removal of the adjacent kidney is not necessary, but en bloc resection of the adrenal, kidney, and regional lymph nodes should be considered if local invasion is present. In primary ACC, it is unlikely that the ACC will invade the liver or adjacent kidney. For larger tumors or when one plans a pulmonary metastasectomy, a thoracoabdominal approach may be necessary. At times, limited hepatic resections, omental and peritoneal debulking, and pulmonary metastasectomy should be considered, particularly in patients with endocrinopathy in which debulking can alleviate symptoms.

For large, right-sided lesions, the IVC is often involved with tumor. If tumor extraction is not feasible, the infrarenal IVC can generally be resected without replacement. For tumor involving the suprahepatic IVC, right atrium, or superior vena cava (SVC), cardiopulmonary bypass or hypothermic circulatory arrest via a thoracoabdominal approach with median sternotomy may be necessary. It is critical to understand the superior extent of the caval tumor burden preoperatively as attempts at extraction or caval clamping can result in massive tumor embolus, resulting in hemodynamic instability or tumor vascularization and growth [7,55–57].

Over the last two decades, laparoscopy has emerged as the preferred approach to the adrenal. Several retrospective, single-center reports as well as a population-based study by the National Surgical Quality Improvement Program (NSQIP) database have suggested that the laparoscopic approach, compared to open resection, is associated with longer operative times but a reduction in operative blood loss, postoperative narcotic requirement, length of stay, and overall morbidity for small, benign adrenocortical tumors [58–61].

As the laparoscopic approach raises the questions about the potential for tumor seeding and fractures, resulting in local and port site recurrences as well as peritoneal carcinomatosis, and as most ACC are large (>10 cm), the role of laparoscopy in the management of ACC remains controversial. However, surgeons are expanding their indications to metastatic disease to the adrenal and ACC. In a multicenter retrospective analysis, Brix et al. [62] evaluated 152 patients with Stage I-III ACC with tumor size ≤10 cm and found that there was no difference in recurrence- or disease-free survival in selected patients. There are currently no randomized trials addressing the role of laparoscopic versus open surgery for the management of ACC.

Postoperative surveillance should continue for many years as recurrence has been reported as long as 10–12 years after resection [1,16,24]. For patients in whom tumors were initially nonfunctional, surveillance should include physical examination and CT at regular intervals. For patients with high preoperative steroid excretion, surveillance should include hormone evaluation (such as DHEAS where DHEAS was initially elevated) as a rise in hormone levels often indicates recurrence prior to physical or radiographic detection. Surveillance is also important for early detection of a second primary cancer, which can occur in up to 24% of patients [63].

**Adjuvant Therapy—Mitotane**

Mitotane (o,p’-DDD or 1,1-dichloro-2(o-chlorophenyl)-2-(p-chlorophenyl)ethane) is an isomer of the pesticide, DDD, and is directly toxic to adrenocortical cells. While the actual mechanism of action is poorly understood, it is believed that it modifies peripheral metabolism of steroids and directly suppresses the adrenal cortex, as accumulation in the zona fasciculata and zona reticularis leads to mitochondrial disruption and necrosis [64].

The use of mitotane in patients with ACC was first reported by Bergensetal. The therapeutic window is narrow and side effects can be dramatic as the drug levels reach the therapeutic range with 8–10 g daily. Up to 80% of patients have gastrointestinal toxicity including nausea, vomiting, and diarrhea. About 40% of patients develop neurologic toxicity, which can result in suicidal depression and treatment discontinuation [26,65,66]. Response is generally seen after 4 weeks, and an average dose of 8.5 g is required for a response. Responses, when present, are temporary with a mean duration of 10.2 months [1].

Even with complete resection, up to 85% of patients will eventually recur and therefore, there is a clear need for adjuvant therapy. Data regarding the role of mitotane in the adjuvant setting are controversial, and there are no prospective, randomized trials published. Early studies failed to show a benefit in disease-free interval or survival when mitotane was given in the adjuvant setting for localized or regional disease [67]. Terzolo et al. reported a retrospective analysis of 177 patients who underwent resection with or without adjuvant mitotane. They reported a significant improvement in recurrence-free survival (RFS) in the adjuvant mitotane group (median RFS 42 months, compared to 10–25 months in the two control groups). Overall survival (OS) was 110 months in the mitotane group, but this varied in terms of statistical significance between control groups. This study has been criticized, and though it is a relatively large series for a rare disease, it is retrospective, nonrandomized, and uncontrolled [68]. While adjuvant mitotane was routinely recommended, only 47 patients were enrolled in the four Italian centers over 20 years, averaging about one patient every other year. The trial was discontinued, and it is not clear if there was an OS benefit. The MDACC group published a retrospective analysis of patients who underwent resection of ACC. They noted a 50% recurrence rate in the index group, which was indistinguishable from the previously cited Terzolo et al. [68] study that reported a 49% recurrence in the setting of adjuvant mitotane [69]. A summary of recent trials addressing the use of mitotane in the adjuvant setting is summarized in Table III. Currently a prospective, multinational, randomized clinical trial is accruing in several European centers and will evaluate the efficacy of adjuvant mitotane therapy versus observation in patients with a low-to-moderate risk of relapse.

**Adjuvant Therapy—Standard Chemotherapy**

Data is lacking on the role of standard chemotherapy in the adjuvant setting for ACC, which can be best summarized by Balasubramaniam and Fojo [49] as “a work in progress.” Two regimens are emerging as options: mitotane in combination with streptozocin (SZ) or in combination with etoposide, doxorubicin, and cisplatin (EDP). A Phase II study by Khan et al. [70] demonstrated that mitotane and Sz given in the adjuvant setting improved disease-free interval and
survival compared to patients who did not receive adjuvant therapy. The EDP regimen has also been evaluated by the same group, but the efficacy of the two regimens has not been formally compared. The First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) trial is currently closed for accrual. The study is a prospective, randomized, controlled, multicenter trial designed to compare the efficiency of EDP plus mitotane versus Sz plus mitotane as first line treatment for Stage III or IV ACC not amenable to radical surgery. The primary endpoint is OS. Data are pending. While this trial addressed the role in the locally advanced and metastatic setting, it will possibly address the efficiency of the two regimens and guide treatment in the adjuvant setting.

It remains unclear if the addition of etoposide and doxorubicin to single agent cisplatin significantly adds to the efficacy of the combination regimen. A Phase II trial by the Southwest Oncology Group demonstrated a 30% response rate with cisplatin and mitotane; the French reported a similar 33% response rate with combination etoposide and cisplatin with 14 of 18 patients also receiving mitotane. There was no overall survival benefit [71,72].

Management of Recurrent or Metastatic Disease

In centers with sufficient experience, consideration should be given to resection of surgically resectable recurrences and metastases as this can be accomplished with limited morbidity [1,5,16]. Data from MSKCC demonstrated that patients undergoing complete resection for recurrent or metastatic disease had a significantly improved median survival of 74 months, compared to 16 months for those with incomplete resection [8]. Mitotane, alone or in combination with standard chemotherapy, remains the standard for unresectable or metastatic ACC. Retrospective analysis of 186 consecutive patients treated at MDACC for ACC demonstrated that 73% of patients developed recurrence during follow-up [73]. Mitotane was given to 67 patients with recurrent ACC, and 19% demonstrated a response. For those who responded, median OS was significantly greater than nonresponders (18 months vs. 9 months). Results of recent trials evaluating mitotane in the locally advanced or metastatic setting are summarized in Table IV.

In terms of the role of standard chemotherapy in the recurrent or metastatic setting, Haq et al. [74] originally published an analysis of 27 trials of various chemotherapeutic regimens given to 12 patients with metastatic disease. Nine patients had previously received mitotane, and all responses were of short duration. Minimal activity was observed with alkylating agents and doxorubicin. Tattersall then reported on the use of cisplatin in the management of four patients with metastatic ACC. A clinical response was observed but failed to be reproduced in the MSKCC experience [75,76]. While we have seen patients with metastatic disease survive >12 months, it remains unclear if this is related to therapy or tumor biology. Abraham et al. conducted a Phase II trial with 36 patients with recurrent or metastatic ACC. Resection was then performed after ≥3 cycles of chemotherapy in patients with stable disease or who demonstrated any response. The study demonstrated a 22% response rate in 35 patients treated with mitotane in combination with doxorubicin, vincristine, and etoposide. However, it did not address whether this regimen was superior to single-agent mitotane [77]. More recently, in a prospective, multicenter Phase II study, 72 patients with metastatic disease not amenable to resection were given EDP in combination with mitotane. There was an overall response rate of 48.6% with five complete

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### TABLE III. Oncologic Outcomes After Adjuvant Use of Mitotane for Adrenocortical Carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution/group</th>
<th>Design</th>
<th>Year</th>
<th>N (Mitotane Group)</th>
<th>Recurrence (%)</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et al.[70]</td>
<td>Sweden</td>
<td>Phase II</td>
<td>2000</td>
<td>17</td>
<td>65</td>
<td>Mitotane-SZ &gt; Control</td>
<td>Mitotane-SZ &gt; Control</td>
</tr>
<tr>
<td>Abiven et al.[86]</td>
<td>France</td>
<td>Retrospective</td>
<td>2006</td>
<td>162</td>
<td>NR</td>
<td>Mitotane &gt; Control</td>
<td>Mitotane &gt; Control</td>
</tr>
<tr>
<td>Terzolo et al.[68]</td>
<td>Germany and Italy</td>
<td>Retrospective</td>
<td>2007</td>
<td>47</td>
<td>49</td>
<td>Mitotane &gt; Control</td>
<td>Mitotane &gt; Control</td>
</tr>
<tr>
<td>Grubbs et al.[69]</td>
<td>MDACC</td>
<td>Retrospective</td>
<td>2010</td>
<td>22</td>
<td>55</td>
<td>Mitotane = Control</td>
<td>Mitotane = Control</td>
</tr>
<tr>
<td>Wangberg et al.[87]</td>
<td>Sweden</td>
<td>Prospective</td>
<td>2010</td>
<td>33</td>
<td>55</td>
<td>All others</td>
<td>NR</td>
</tr>
</tbody>
</table>

Adapted from Reference [22].

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### TABLE IV. Oncologic Outcomes After Mitotane for Locally Advanced or Metastatic Adrenocortical Carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution/group</th>
<th>Design</th>
<th>Year</th>
<th>N</th>
<th>Response (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venkatash et al. [88]</td>
<td>MDACC</td>
<td>Retrospective</td>
<td>1989</td>
<td>72</td>
<td>29</td>
<td>PR only</td>
</tr>
<tr>
<td>Luton et al.[89]</td>
<td>France</td>
<td>Retrospective</td>
<td>1990</td>
<td>37</td>
<td>13</td>
<td>PR only</td>
</tr>
<tr>
<td>Decker et al.[90]</td>
<td>ECOG</td>
<td>Prospective</td>
<td>1991</td>
<td>36</td>
<td>22</td>
<td>PR + CR</td>
</tr>
<tr>
<td>Pommier and Brennan [6]</td>
<td>MSKCC</td>
<td>Retrospective</td>
<td>1992</td>
<td>29</td>
<td>24</td>
<td>PR only</td>
</tr>
<tr>
<td>Haak et al.[91]</td>
<td>Holland</td>
<td>Retrospective</td>
<td>1995</td>
<td>55</td>
<td>27</td>
<td>PR + CR</td>
</tr>
<tr>
<td>Barzon et al.[92]</td>
<td>Italy</td>
<td>Retrospective</td>
<td>1997</td>
<td>11</td>
<td>18</td>
<td>PR</td>
</tr>
<tr>
<td>Williamson et al.[93]</td>
<td>SWOG</td>
<td>Phase II</td>
<td>2000</td>
<td>16</td>
<td>13</td>
<td>PR</td>
</tr>
<tr>
<td>Khan et al.[70]</td>
<td>Sweden</td>
<td>Phase II</td>
<td>2000</td>
<td>11</td>
<td>36</td>
<td>PR + CR</td>
</tr>
<tr>
<td>Baudin et al.[94]</td>
<td>France</td>
<td>Prospective</td>
<td>2001</td>
<td>13</td>
<td>33</td>
<td>PR + CR</td>
</tr>
<tr>
<td>Gonzalez et al. [73]</td>
<td>MDACC</td>
<td>Retrospective</td>
<td>2007</td>
<td>67</td>
<td>19</td>
<td>PR + CR</td>
</tr>
</tbody>
</table>

Adapted from Reference [22].

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Milotane-Sz.
responses (CR) and 30 partial responses (PR). OS was 28.5 months in the entire cohort and 47.7 months in those achieving a disease response [78].

Management of Hormonal Excess

In many patients, advanced disease at presentation precludes resection. While chemotherapy is often administered, persistent hormonal excess results in severe sequelae. Mitotane, ketoconazole, metyrapone, and etomidate may be used to alleviate hormonal symptoms. Based on the observation that ketoconazole caused gynecomastia, it was found that this imidazole-derived, broad-spectrum antifungal could inhibit steroid synthesis via inhibition of C17-20 desmolase. Dosing begins as 200 mg three to four times daily for patients with Cushing’s syndrome or ACC and can be gradually, incrementally increased to 1,200–1,600 mg three to four times daily (maximum daily dose: 3,600–6,400 mg). Toxicities include hepatotoxicity, nausea, vomiting, abdominal pain, alopecia, hypertension, contact dermatitis, gynecomastia, adrenal insufficiency, hypothyroidism, hypertriglyceridemia, and an erythema multiforme-like syndrome. Ketoconazole is a cytochrome P450 inhibitor, and drug toxicity can increase when given with doxorubicin, etoposide, taxanes, and vinca alkaloids [79].

Metyrapone reduces cortisol and aldosterone production via inhibition of cortical 11β-hydroxylase. Dosing starts as 500–1,000 mg in two to three divided doses and can incrementally increased. There is little clinical benefit beyond 2,000 mg daily. Metyrapone inhibits a distal step in the steroid biosynthesis pathway; precursors such as 11-deoxycortisol increase and obviate the need for mineralocorticoid repletion. Common toxicities include hypertension, alopecia, hirsutism, acne, nausea, and abdominal discomfort. Metyrapone is also a cytochrome P450 inhibitor.

Etomidate is an imidazole-derivative that is used as an ultrashort-acting, nonbarbiturate hypnotic but also inhibits 11β-hydroxylase and cholesterol side-chain cleavage, resulting in reduction of cortisol and aldosterone synthesis. Dosage begins at 0.1–0.3 mg/hr continuously infused intravenously or 0.2–0.6 mg/kg infused intravenously as bolus. The maximum daily dose is 25 mg/kg. Common toxicities include sedation, hypotension, and myoclonus.

Alternative Therapies

Due to the high risk of local recurrence after potentially curative resection, radiation has been proposed as an adjunct. Whereas earlier studies failed to show a benefit, a retrospective analysis of patients who received adjuvant radiotherapy to the tumor bed demonstrated a significant reduction in local recurrence from 79 to 19%; however, this did not translate into improved disease-free or OS [80]. A recent meta-analysis of 10 studies addressing radiation in both the adjuvant and palliative settings reported local control rates of 0–86% without clear information on indications, survival, delivered dose and target, or completeness of resection. The study concluded that adjuvant radiotherapy to the tumor bed should be considered for patients at high risk of local recurrence (i.e., R1 resection, locally advanced disease without residual disease after primary resection). However, adjuvant radiation therapy is currently not recommended given the lack of evaluable evidence. In the palliative setting, good symptom control of metastatic disease can be achieved with radiation, particularly for bone metastases with spinal cord compression, cerebral metastasis, and superior or IVC obstruction [81].

Arterial embolization has been reported as a means of controlling metastatic liver disease. Data are limited in terms of oncologic outcomes, but this technique may be considered when trying to achieve response or stabilization of metastatic disease to the liver, particularly in symptomatic patients [1,82,83].

Adrenocortical Carcinoma: Past, Present, Future

OUTCOMES

Improved survival is demonstrated in patients with early stage tumors and after complete resection. In an MSKCC series of 113 patients with ACC, median OS was 38 months (5-year survival: 37%). When analyzed by stage, patients with Stage I or II disease had a median survival of 101 months (5-year survival: 60%), which compared favorably to those with Stage III or IV disease (median survival: 15 months, 5-year survival: 10%; Fig. 3) [8]. Furthermore, complete primary resection was associated with a more favorable outcome with a median survival of 74 months, compared to 12 months for those who underwent incomplete resection (5-year survival 55% and 5%, respectively; Fig. 4).

In institutions with sufficient experience in recurrent or metastatic ACC, re-resection should be considered for patients with resectable abdominal recurrences or metastases. For patients with a complete re-resection (47 of 113 in the previously cited study), median survival was 74 months compared to 16 months for those with incomplete re-resection (5-year survival: 57 versus 0%; Fig. 5) [8]. Various analyses have attempted to identify demographic or pathologic markers that correlate with oncologic outcome. Stojadinovic et al. reported that significant predictors of ACC-specific survival on multivariate analysis include presence of distant metastases at time of initial presentation, adjacent organ invasion, and high mitotic rate (>5 mitoses/HPF). When multivariate analysis was performed for primary ACC without synchronous metastases, only high mitotic rate remained an independent predictor of survival [52]. Bilimoria et al. recently reported results from 3,982 patients with ACC from the National Cancer Data Base. They reported an increased risk of death with age >55 years, poorly differentiated histology, positive margins, resection involving an adjacent organ, and the presence of nodal or distal metastases [15].

RECENT ADVANCES AND THE FUTURE OF ACC

Survival from ACC has not changed over the last 20 years. Systemic treatment, till date, is unsatisfactory. Advances are hindered by disease heterogeneity, a poor understand of pathogenesis, and rarity of the tumor [15]. Not a single Phase III randomized, control trial has been published on ACC. Future research endeavors should establish standards for treatment and explore alternative treatment options including targeted therapies.

A randomized controlled trial is now underway to address the role of mitotane in the adjuvant setting. Additionally, the Phase III FIRM- ACT trial, sponsored by the Collaborative Group for Adrenocortical Cancer (COACT), will determine the efficiency of combina-

Fig. 3. Disease-specific survival, based on stage of presentation with adrenocortical carcinoma.
combination of cixutumumab and temsirolimus (an mTOR inhibitor), advanced cancer including ACC, the first Phase I trial evaluating the
In an attempt to enhance mTOR-targeted activity in patients with
IGF-1R) in patients with recurrent, metastatic, or unresectable ACC.
without cixutumab (IMC-A12; a monoclonal antibody against
an target of rapamycin (mTOR) and the RAS-RAF-MAP kinase
pathways, which mediate cell survival and proliferation, respectively.
Upregulation of stimulatory ligand IGF2 and ultimately, upregulation
of the disease, it is possible that targeted agents will play an
increasing role in the management of ACC. As previously stated,
IGF-1R signaling occurs via two pathways: The PI3K-Akt-mammali-
an target of rapamycin (mTOR) and the RAS-RAF-MAP kinase
pathways, which mediate cell survival and proliferation, respectively.
Upregulation of stimulatory ligand IGF2 and ultimately, upregulation
of these two pathways via IGF-1R, have been implicated in the
pathogenesis of ACC. Therefore, therapies targeting the IGF path-
way, as well as other altered growth factors and cytokines, could be
promising [84,85].
Haluska et al. conducted a Phase I trial evaluating the anti-IGF-
1R antibody, figitumumab. In patients with refractory ACC, this
therapy was well tolerated, and disease stability was achieved in
57% of patients [86]. The GALACCTIC trial is an ongoing random-
zized, double-blind, placebo-controlled Phase III trial evaluating OSI-
906 (linsitinib), a dual inhibitor of both IGF-1R and insulin receptor,
was performed and demonstrated that the combination was well
tolerated [87]. Results of these and future trials will define whether
targeted therapies against the IGF pathway improve oncologic
outcomes in patients with ACC.

Additionally, there are ongoing Phase II trials evaluating bevacizumab, sunitinib, and sorafenib for both first- and second-line
therapy in advanced ACC. As drug resistance is a problem in ACC
and as MDR1 expression has been found to induce cytotoxic drug
resistance in in vitro studies, the NCI is currently sponsoring a Phase
II trial that will incorporate tariquidar (XR9576), a third generation
noncompetitive inhibitor of the MDR1 efflux pump, in an attempt to
overcome this obstacle [22,88,89].

Management of patients with ACC continues to represent a
clinical challenge. We rely on scant evidence, clinical judgment, and
biological rationale. As we move into the future, there is a need for
ongoing study into the pathogenesis and treatment of ACC. Collaborations, incorporating those involving translational research
and clinical trials with biological correlates, will ideally lend the
way to new insights that will guide future therapies and improve
outcomes.

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