Adrenal Cortical Carcinoma

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Current Treatment Options in Oncology 2001, 2:355–364
Current Science Inc. ISSN 1527-2729
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Opinion statement

Adrenal cortical carcinoma is a rare endocrine tumor, and complete surgical resection is the only potentially curative treatment. Accurate preoperative biochemical and radiographic evaluation of the patient who presents with an adrenal mass optimizes patient management and facilitates a complete margin-negative resection of the primary tumor—the most important prognostic variable for long-term survival. Response to mitotane or chemotherapy is modest in patients with advanced disease. It is hoped that an improved understanding of the molecular pathogenesis of this challenging tumor will lead to the development of novel treatment strategies.

Introduction

The adrenal cortex is responsible for synthesizing and secreting several different classes of hormones, including glucocorticoids, mineralocorticoids, and sex steroids. These hormones, which consist mainly of cortisol, aldosterone, dehydroepiandrosterone (DHEA), and their biologically active metabolites, play essential roles in regulating multiple processes throughout the body. They include glucose metabolism, fluid-electrolyte balance, inflammation, wound healing, and sexual development. Fortunately, adrenal cortical cancers are uncommon, with a worldwide incidence approaching two cases per million. The two most commonly affected groups are children less than 5 years of age and adults in their fourth and fifth decades of life [1]. A slight gender predominance is also observed: women demonstrate an increased incidence (58.6%) compared with men (41.4%) [2]. This may in part be explained by the increasing incidence of cigarette smoking and oral contraceptive use in females—both factors previously linked with adrenal cortical tumorigenesis.

The clinical presentation of adrenal cortical neoplasms varies depending on the size and hormonal secretory status of the tumor. Patients with large tumors often present with abdominal pain and pressure due to a mass effect, and they may report other symptoms such as weight loss, malaise, dyspnea, hematuria, and varicocele. Excessive hormone production and secretion is observed in more than 50% of patients. These functional tumors most commonly secrete cortisol (30%), androgens (20%), estrogen (10%), and aldosterone (2%), whereas 35% of patients secrete a mixed pattern of hormones [3]. Large proportions of nonfunctional adrenal cortical tumors are serendipitous findings unrelated to the clinical presentation of the patient and are appropriately termed incidentalomas. Incidentalomas are relatively common, occurring in up to 4% of individuals undergoing abdominal computed tomography (CT), and in up to 7% of individuals at autopsy [4••]. Most commonly, these tumors are smaller than 6 cm and represent benign, nonfunctional, adrenal cortical adenomas.

Once a clinical diagnosis of an adrenal tumor is suspected based on patient history or radiologic findings, it is important to determine whether the neoplasm is functional or nonfunctional, benign or malignant, and, in the case of malignant tumors, whether the adrenal neoplasm is a primary lesion or a secondary metastatic focus. To determine the hormonal secretory status of an adrenal tumor, a careful history and physical examination looking for clinical features suggestive of Cushing's syndrome, hypertension, and virilization should be performed. A rapid office biochemical evaluation that initially involves a random afternoon plasma sample to measure circulating cortisol and electrolyte levels and a 24-hour urine collection to measure vanillylmandelic acid, metanephrine, and catecholamine concentrations should be obtained. The patient is administered oral

dexamethasone (1 mg) at 10 PM the same evening and is instructed to return to the clinic the following morning at 8 AM to determine serum cortisol concentration. In the afternoon, the patient returns the timed 24-hour urine collection specimen. If the patient's serum cortisol level is not suppressed below 5 μg/dL, a second 24-hour urine collection is performed to measure cortisol, 17-hydroxysteroid, and 17-ketosteroids. Hypokalemia is suggestive of aldosterone excess; elevated cortisol levels that cannot be suppressed with dexamethasone suggest a cortisol excess; abnormal urine 17-ketosteroids suggest a masculinizing or feminizing tumor; and elevated urine catecholamine and metanephrine concentration raise suspicion of a pheochromocytoma.

The size of a unilateral adrenal tumor as measured on CT or magnetic resonance imaging (MRI) remains the best indicator of malignancy. It is estimated that an adrenal mass larger than 6 cm in diameter has a 35% to 98% likelihood of being an adrenal cortical carcinoma [5]. In contrast, large adrenal adenomas (greater than 6 cm) are uncommon, although the exact frequency is unknown. Although malignancy cannot be ruled out in tumors between 3 and 5 cm in diameter, specific radiologic features can be important. CT characteristics of malignancy include tumor inhomogeneity, irregular shape, and irregular margins. MRI characteristics of malignancy include signal intensity on T2-weighted images: adenomas have low signal intensity compared with liver (adrenal mass/liver ratio 1.4); cortical carcinomas and metastasis are moderately bright (adrenal mass/liver ratio 1.2–2.8); and pheochromocytomas are very bright (adrenal mass/liver ratio 3) [6]. Unfortunately, the use of signal intensity ratios to differentiate benign from malignant neoplasms may be unreliable because these ratios overlap in up to 40% of cases. Percutaneous biopsies of the adrenal mass should be avoided unless metastatic disease is suspected. Lung cancer is the most common primary tumor to metastasize to the adrenal gland, whereas cancer of the breast, stomach, prostate, kidney, colon, and melanoma can metastasize to the adrenals. Patient symptoms, previous history of cancer, physical examination findings, and radiologic or biochemical tests often suggest the origin of the underlying malignancy; however, occult primary malignancies can occur.

Treatment

Pharmacologic treatment

- In patients with corticosteroid-producing tumors, careful attention must be given to ensure adequate corticosteroid coverage and replacement during the perioperative and postoperative period because suppression of the contralateral gland can be expected. Perioperative steroids should also be considered in patients with nonfunctional tumors to compensate for any steroidal production by the tumor.
- The dose and duration of replacement must be individualized and can vary depending on the tumor. For example, patients presenting with Cushing's syndrome may take longer to regain adequate steroid production in the contralateral adrenal gland. Steroid replacement during the perioperative period should resemble that administered to patients receiving long-term exogenous steroids prior to surgery (*eg*, 100 mg of hydrocortisone intravenously on call to the operating room and continued every 8 hours until a tapering regimen is commenced).
- Mineralocorticoid replacement should also be considered in patients with total adrenal ablation. Although corticosteroids exhibit mineralocorticoid effects, this compensatory response may not be sufficient, and patients may need to be administered synthetic adrenocorticoid fludrocortisone acetate. The dosing regimen needs to be individualized based on the patient's weight gain and serum electrolytes. However, an initial dose of 0.1 mg three times a week can be given and adjusted up to a dose of 0.1 mg/d. All patients with aldosterone-producing adrenal tumors must have their blood pressure controlled and their potassium levels monitored before surgery.

Table 1. Survival from reported series of patients undergoing potentially curative resection for adrenocortical carcinoma

Study	Institution	Year	Patients, *n*	Margin analysis	Follow-up	Survival	
						Overall, *mo*	5-year actuarial, %
Harrison *et al.* [23••]	MSKCC	1999	46	No	20	28†	36
Khorram-Manesh *et al.** [24]	Sweden	1998	18	No	85	--	58
Crucitti *et al.* [25]	Italy	1996	91	No	--	28‡	48
Lee *et al.** [26••]	MDACC	1995	16	Yes	43	46†	46
Zografos *et al.* [27]	Roswell Park	1994	15	No	--	13†	38
Haak *et al.* [9]	Netherlands	1994	47	No	--	--	49
Icard *et al.** [3]	France	1992	127	No	--	--	42
Icard *et al.* [28]	France	1992	31	No	--	44‡	45
Pommier *et al.** [29]	MSKCC	1992	53	No	28	28‡	47
Soreide *et al.* [30]	Norway	1991	99	No	--	--	16
Gröndal *et al.** [31]	Sweden	1990	22	No	--	--	--
Henley *et al.* [32]	Mayo Clinic	1983	31	No	--	--	32

* Includes patients that underwent resection of synchronous metastatic disease.
† Median.
‡ Mean.
MDACC—MD Anderson Cancer Center; MSKCC—Memorial Sloan-Kettering Cancer Center.

- Administration of spironolactone, an aldosterone antagonist, for 3 to 4 weeks before surgery has been the mainstay of medical treatment in patients with aldosterone-producing adrenal tumors. Although several doses have been reported in the literature ranging from 25 to 400 mg/d, this drug is associated with considerable side effects at higher doses (more than 100 mg/d). These side effects include gastrointestinal symptoms, impotence, fatigue, and gynecomastia. It is advisable to limit doses below 50 mg/d, especially in men. Spironolactone can be used in combination with other antihypertensive medications, including angiotensin-converting enzyme inhibitors and calcium channel blockers.

Surgery

- Hormone-secreting adrenal cortical tumors and hormonally silent adrenal masses 5 cm or more in diameter or with a suspicious appearance on imaging should be surgically excised. For a malignant adrenal cortical mass, radical surgical excision with en bloc resection of any locally invaded structures offers the patient the greatest potential for cure (Table 1), especially in children and adult patients with stages I and II tumors (Table 2). In patients with stages III and IV disease, the role of surgery remains more controversial; several of the studies outlined in Table 1 clearly indicate no overall improvement in patient survival, especially in patients presenting with metastatic disease in which death usually occurs within 1 year. The presence of inferior vena cava (IVC) extension should not be considered metastatic disease and warrants a more aggressive surgical procedure that should include an attempt at removing the intravascular extension.

Table 2. TNM classification of adrenal cortical carcinoma

Tumor	Nodes	Metastasis
T1 Tumor < 5 cm, no invasion of surrounding tissue	N0 No lymph nodes involved	M0 No distant metastases
T2 Tumor > 5 cm, no invasion	N1 Regional lymph nodes involved	M1 Distant metastases
T3 Local tumor growth without infiltration of adjacent organs		
T4 Infiltration of surrounding organs		
Stages		
I T1 N0 M0		
II T2 N0 M0		
III Regional extension and or N1		
IV Distant metastasis		

Adapted from Sullivan *et al.* [33] and MacFarlane [34].

- Laparoscopic adrenalectomy via a transperitoneal or retroperitoneal approach has become the preferred treatment for presumed benign adrenal cortical nonfunctional and functional tumors [7]. Although patients undergoing laparoscopic resection demonstrate reduced hospital stay, lower morbidity, and faster recovery, several factors, including tumor size, malignancy, and surgeon experience, may limit the use of minimally invasive surgery. If a preoperative diagnosis of adrenal cortical carcinoma is suspected, the surgeon must select an operative approach that will maximize the likelihood of achieving a margin-negative resection.
- For adrenal cortical carcinomas less than 10 cm, we recommend a transabdominal approach through a subcostal incision to remove the suspected adrenal cortical malignancy. This approach allows adequate exposure to the tumor mass and common sites of metastasis, including the liver, omentum, periaortic nodes, and peritoneum. It also allows for vascular control of the IVC, aorta, and renal vessels when necessary. Local tumor invasion is common and may require the en bloc excision of contiguous structures, including the kidney, liver, IVC, spleen, pancreas, and regional lymph nodes. Extreme care should be taken not to violate the tumor to minimize tumor spillage and the chance of local tumor recurrence. Right adrenal cortical carcinoma frequently invades the posterior segment of the right hepatic lobe and IVC. Limited hepatic resection for metastasis and excision of omental or peritoneal implants are justified and may provide the patient with some symptom relief due to hormone excess. For larger lesions greater than 10 cm, a thoracoabdominal approach often provides better access to the tumor; and, in the case of right adrenal tumors, it allows for better hepatic mobilization and control of the suprahepatic IVC if necessary. For lesions with intracaval extension, cardiac bypass is required if the lesions extend above the subhepatic vena cava and into the right atrium. Prior knowledge of the superior extent of the lesion is needed to prevent a tumor embolus at the time of clamping of the IVC, which may result in hemodynamic instability or neovascularization and growth in the lung.
- Based on anatomic location, local invasion of arterial structures occurs more commonly with left adrenal cortical carcinoma. Tumor encasement of the celiac axis, aorta, or proximal superior mesenteric artery precludes surgical resection. The proximity of the tumor to important vascular structures should be apparent on contrast-enhanced CT images. Intraoperative assessment for local vascular invasion is extremely difficult: it may be associated with iatrogenic arterial injury; and, when incorrect, is likely responsible for the high incidence of incomplete tumor resection.

Table 3. Adrenal cortical carcinoma response to mitotane therapy

Study	Institution	Year	Patients, *n*	Result/conclusion
Kasperlik-Zaluska *et al.* [12]	Poland	1995	36	Suggested benefit with adjuvant mitotane treatment
Haak *et al.* [9]	Netherlands	1994	62	Response rate 21% (6 of 29)
Vassilopoulou-Sellin *et al.* [11]	MDACC	1993	13	No effect on survival
Pommier *et al.* [29]	MSKCC	1992	29	PR 24%
Luton *et al.* [10]	France	1990	37	PR 22%, no effect on survival
Venkatesh *et al.* [35]	MDACC	1989	72	Stable disease or PR 29%
Karakousis *et al.* [36]	Roswell Park	1985	10	Stable disease or response 40% ($n = 4$)
van Slooten *et al.* [37]	Netherlands	1984	34	Serum level > 14 μg/mL associated with improved survival
Henley *et al.* [32]	Mayo Clinic	1983	24	PR 4% ($n = 1$)

MDACC—MD Anderson Cancer Center; MSKCC—Memorial Sloan-Kettering Cancer Center; PR—partial response.

- Postoperative follow-up should include a physical examination, biochemical assessment if the tumor was functional, CT scan, and chest radiograph every 4 months following a potentially curative resection for primary tumor. Bone metastasis is often symptomatic and should be suspected in patients with elevated alkaline phosphatase levels. In patients that remain disease free, the duration of radiologic surveillance remains unclear. The authors advocate continued CT scanning beyond 5 years after diagnosis due to unpredictable biologic behavior of these tumors. In patients presenting with an isolated tumor recurrence amenable to reoperation, surgery should be recommended and the tumor resected. In patients presenting with recurrence in multiple sites, systemic therapy may prolong overall survival.

Systemic therapy

- Several studies have demonstrated a beneficial role for mitotane (ortho, para-DDD, or 1,1-dichloro-2-[o-chlorophenyl]-2-[p-chlorophenyl] ethane) as adjuvant therapy in the treatment of adrenal cortical carcinoma (Table 3). Mitotane acts via several different mechanisms, including reducing corticoid biosynthesis by preventing cholesterol side chain cleavage and 11-β hydroxylation. It also induces structural damage to mitochondria in the zona reticularis and zona fasciculata, leading to necrosis of both normal and tumor tissue [8•]. These actions appear to be dose dependent: doses less than 3 g/d lead to marked suppression of adrenal steroid secretion, and doses greater than 3 g/d produce an adrenolytic effect. Typically, initial daily dosing begins with the administration of 1.5 to 2 g divided into three or four doses. The daily dosage is gradually increased to 8 to 12 g/d to achieve a target serum level above 15 μg/L [8•]. This threshold is based on previous studies that demonstrated a correlation between plasma serum levels and survival, with the best response seen in patients with serum levels greater than 14 μg/mL [9]. Typically, serum levels reach a plateau after approximately 8 to 10 weeks of treatment and persist for 6 to 9 weeks after discontinuation of the drug due to extensive storage in adipose tissue. Glucocorticoid replacement should commence simultaneously (nonfunctional tumors) or within 2 to 4 weeks (functional tumors) after commencing mitotane due to the suppressive effects on healthy adrenal tissue. A dose of hydrocortisone, 20 to 40 mg, is recommended, with two thirds of the dose

administered in the morning and the remainder administered in the afternoon. The exception to this is during the perioperative phase, when higher doses may be required. Mineralocorticoid replacement with fludrocortisone may also be indicated depending on serum electrolyte measurements. Once mitotane treatment has been terminated, no attempt at tapering the corticosteroid replacement dose should be attempted for at least 1 month.

- In general, mitotane treatment is associated with frequent and serious side effects that appear to be dose dependent. The most common side effects are gastrointestinal symptoms (*eg*, nausea, vomiting, and anorexia) and diarrhea, which occurs in more than 80% of patients. Neuropsychiatric symptoms, including ataxia, dysarthria, confusion, lethargy, and somnolence, occur in less than 25% of patients, and skin rashes have also been reported in approximately 10% of patients. Other infrequent side effects include hepatotoxicity and hypercholesterolemia. All side effects can be reversed or reduced by reducing the dose of mitotane or by interrupting therapy, although, as previously mentioned, serum levels can remain elevated for a substantial period.
- Anecdotal reports and retrospective studies involving small series of patients have yielded conflicting results concerning the efficacy of mitotane, either as adjuvant therapy or for the treatment of locally unresectable or metastatic disease (Table 3). In the classic study by Luton *et al.* [10], mitotane therapy had no significant effect on survival but was effective in controlling hormone secretion in 75% of patients with adrenal cortical carcinoma. In a similar report by Vassilopoulou-Sellin *et al.* [11], no improvement in survival was observed in eight patients treated with mitotane treatment. In fact, only one of the eight patients that received mitotane remained disease-free 2 years after diagnosis. These observations were in marked contrast to other studies that demonstrated improved survival [9,12], including cases of complete remission for up to 4 years. Although there are currently no prospective studies available, the collective findings from both anecdotal and retrospective studies suggest a putative role for mitotane in the treatment of adrenal cortical cancer. The challenge involves attempting to translate information from this body of literature into clinical practice, which is further complicated by several factors: 1) differing endpoints studied in the various studies, which makes direct comparisons difficult (*ie*, survival versus hormone production); 2) non–protocol-based therapy, which often involves using differing treatment regimens of mitotane, often in combination with various other cytotoxic agents that are administered at different times following the surgery; and 3) failure to measure serum levels of mitotane, which appear to correlate with treatment response.
- Chemotherapeutic agents have been shown to be of some benefit in patients who do not respond to mitotane, who experience intolerable side effects while administered mitotane, or who present with unresectable tumors or recurrent tumors (Table 4). Cisplatin-based therapy in combination with other cytotoxic agents has been most commonly reported to be effective in several small patient series. For example, cisplatin administered in a dose of 100 mg/m^2 on day 1 and etoposide in a daily dose of 100 mg/m^2 on days 1 through 3 resulted in three complete and three partial response rates in 18 patients, for an overall response rate of 33% [13]. Similar response rates were observed in patients treated with combination 5-fluorouracil, doxorubicin, and cisplatin [14].

Table 4. Adrenal cortical carcinoma response to chemotherapy

Study	Institution	Year	Patients, *n*	Regimen	Response
Abraham *et al.* [38]	NCI	1999	28	M E D V	CR 1, PR 4
Berruti *et al.* [39]	Italy	1998	28	M E D P	CR 2, PR 13
Zidan *et al.* [40]	Israel	1996	1	E P*	PR 1
Bukowski *et al.* [41]	SWOG	1993	37	M P	PR 11
Berruti *et al.* [16]	Italy	1992	2	E D P	PR 2
Schlumberger *et al.* [14]	France	1991	13	D P 5-FU	CR1, PR 2
Hesketh *et al.* [42]	Boston Un75iversity	1987	4	E P B	CR 1, PR 1
Johnson *et al.* [43]	Vanderbilt	1986	2	E C	PR 2

* Mitotane failure.
B—bleomycin; CR—complete resection; D—doxorubicin; E—etoposide; 5-FU—5-fluorouracil; M—mitotane; NCI—National Cancer Institute; P—cisplatin; PR—partial response; SWOG—Southwest Oncology Group; V—vincristine.

- The heterogeneous response to classic cytotoxic chemotherapy can in part be explained by the expression of the multidrug resistance-1 gene and its protein product, P-glycoprotein, that is frequently expressed on the surface of malignant adrenal cells. P-glycoprotein is an adenosine triphosphate-binding cassette that is able to actively transport chemotherapeutic agents out of the cell, thereby conferring chemotherapy resistance. Interestingly, mitotane has been shown to act as a P-glycoprotein antagonist in vitro [15], suggesting that mitotane therapy may enhance the tumorolytic effect of classic cytotoxic chemotherapeutic agents. This approach has been evaluated by Berruti *et al.* [16], who treated 28 patients with advanced inoperable disease with combination etoposide, doxorubicin, and cisplatin (EDP). The EDP schedule (etoposide, 100 mg/m^2 on days 5 through 7; doxorubicin, 20 mg/m^2 on days 1 and 8; cisplatin, 40 mg/m^2 on days 2 and 9) was repeated every 4 weeks and repeated for a maximum of six cycles. Mitotane was started at 1 g/d and escalated to 4 g/d or the maximum dose tolerated, which usually was less than 4 g due to the side effects of this combination. Complete response was achieved in two patients and a partial response in 13, for an overall response rate of 53.5%. The median time to disease progression in responding patients was 24 months. These results are encouraging and support the concept of combining classic cytotoxic agents with mitotane.
- Further substances that have been tested in humans include octreotide, suramin, and gossypol. Octreotide is a potent somatostatin analogue that inhibits the secretion of several growth factors that promote the growth of adrenal cortical cells. However, initial use of octreotide in a single patient with advanced adrenal cortical cancer lacked any significant effect [17]. Arlt *et al.* [18] reported data from nine patients with metastatic adrenal cortical cancer treated with suramin, a polysulfated napthylurea. Three patients achieved a partial response, two exhibited disease stabilization, and four patients demonstrated disease progression. Unfortunately, many of these patients developed potentially life-threatening side effects during the course of their treatment, including coagulopathy (six patients), thrombocytopenia (six patients), polyneuropathy (two patients), and allergic skin reactions (four patients), thereby excluding further human use of this drug. Use of gossypol, a biphenolic derivative extracted from cottonseeds, has also been used to treat metastatic adrenal cortical carcinoma. This drug had a 14% partial tumor response that lasted for several months and up to 1 year [19]. The drug was well tolerated with

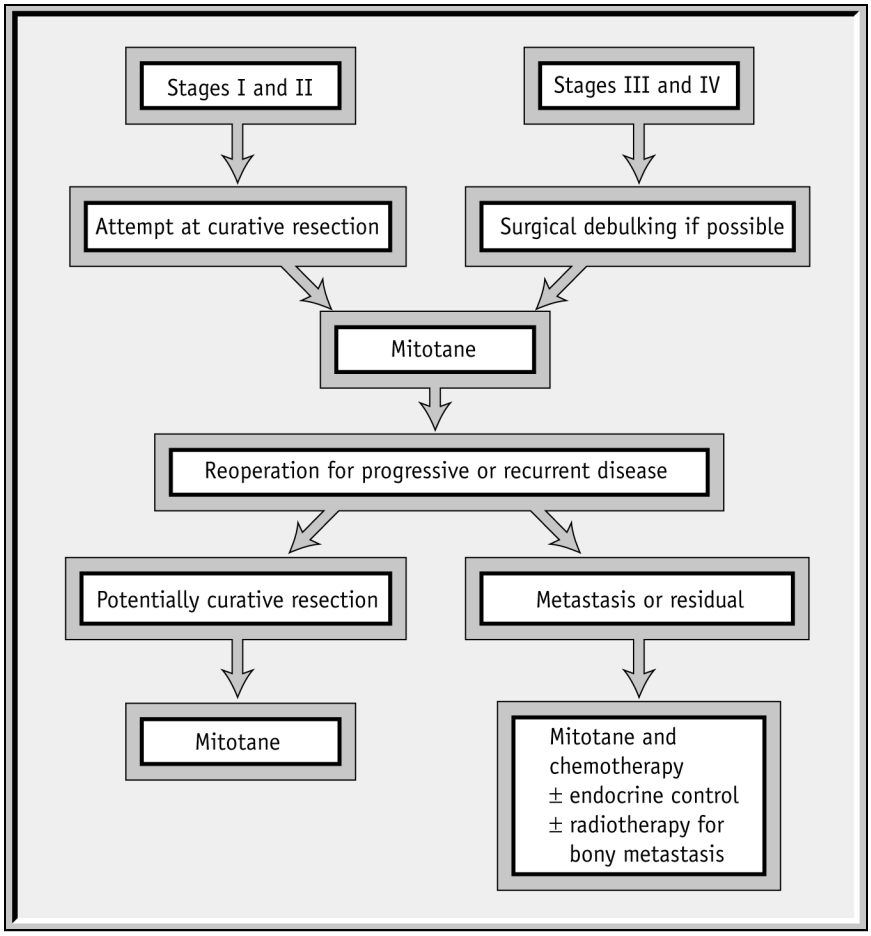

Figure 1. Treatment algorithm for patients with adrenal cortical carcinoma.

few side effects and is currently available for treatment on an outpatient basis. Treatment of the human NCI-H295 adrenal cortical carcinoma cell line with paclitaxel, an agent that reversibly binds the beta subunit of tubulin, resulted in a dose-dependent inhibition of cell proliferation and induction of cellular apoptosis [20]. Future clinical trials are needed to assess the efficacy of paclitaxel in vivo.

- Additional pharmacologic agents are available for inhibiting the endogenous production of steroids, especially in patients that have undergone unsuccessful surgery and mitotane therapy. Ketoconazole is an imidazole antifungal agent that is able to suppress androgen and corticosteroid production but does not inhibit tumor growth. Ketoconazole treatment results in long-term hormonal suppression and can be administered preoperatively to patients with Cushing's disease and adrenal cortical carcinoma [21]. The maximal daily dose is 200 mg four times daily and requires routine measurements of liver transaminases to monitor for liver toxicity. Therapy should be temporarily disrupted in patients who exhibit elevated liver enzymes. Metyrapone is another pharmacologic agent that is able to inhibit adrenal cortisol production when the combination of mitotane and ketoconazole fail [22]. Doses range from 750 to 5000 mg/d and result in suppression of normal adrenal tissue, making it essential to provide patients with hydrocortisone replacement. Figure 1 provides the reader with an algorithm for treating patients with adrenal cortical cancer. A randomized trial examining the adjuvant use of mitotane and other chemotherapeutic agents appears warranted.

External beam radiotherapy

- Most reports in the literature suggest that external beam radiotherapy administered as adjuvant treatment after complete surgical resection is ineffective in the treatment of patients with adrenal cortical carcinoma and does not improve overall survival. However, palliative irradiation for painful bone metastasis is considered standard therapy.

Emerging therapies

- Better systemic therapies with fewer side effects are clearly needed before major improvements in overall survival can be observed. Several agents, including paclitaxel, have been effective in reducing tumor growth in vitro but have yet to be studied extensively in humans.
- Molecular genetic studies in humans with adrenal cortical cancer have identified several potential genes that may be involved in tumor progression. These include the p53 tumor suppressor gene, mutations in G-protein–coupled receptors, and increased expression of several growth factors. A better understanding of these various genetic events may allow us to better predict tumor response to various adjuvant therapies and overall patient prognosis.
- Minimally invasive surgery has become the standard surgical technique for resecting nonmalignant adrenal cortical lesions and for some patients with metastatic disease.

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