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Adrenocortical carcinoma

Abstract Adrenocortical carcinoma is rare, tends to occur in the first decade as well as the fourth and fifth decades of life, and is slightly more common in women. The tumors are classified as functional or nonfunctional, depending on tumor production of corticosteroid, androgen, estrogen, or mineralocorticoid. Most patients present with large masses and with stage IV disease. Abdominal computerized tomography and magnetic resonance imaging are used in the evaluation of intra-abdominal disease. The most effective treatment for adrenocortical carcinoma is complete resection. Surgical resection remains the only potentially curative treatment for this disease. Early stage and curative resection are the two clinical factors that are of prognostic significance for long-term survival. Mitotane is the chemotherapeutic agent most often used to treat adrenocortical carcinoma. Its efficacy in prolonging survival is limited but may be enhanced by monitoring of serum levels and their maintenance at elevated values. Even for patients who undergo complete resection, recurrent and metastatic disease are extremely common. The only effective treatment for recurrent disease is reoperation.

Incidence

Adrenocortical carcinoma is a rare tumor with an annual incidence of between 0.5 and 2 cases per million [2, 29]. This contrasts with the incidence of adenomas of the adrenal gland. As many as 2% of all autopsies show adenomatous change in the adrenal gland [2].

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Demographics

There is a bimodal occurrence by age, with one peak occuring at less than 5 years of age and a second peak, in the fourth and fifth decades [20, 26]. Most series find a slight preponderance of female patients but some find a male predominance [23, 28]. In a review of the English literature between 1952 and 1992, Wooten and King [31] found 87 series containing 1891 patients. There was a slight female (4:3) predominance. The incidence of carcinoma on the left side was 52.8% and in 2.4% of cases it was bilateral. The overall incidence of functional lesions was 59.3%. More often than males, females with adrenocortical carcinoma developed functional tumors. If tumors are functional in males, they tend to occur before the age of 20 years, and most nonfunctional tumors tend to occur in men over the age of 40 years [3].

Etiology

The etiology of adrenocortical carcinoma is unknown. It has been argued that the carcinoma develops from hyperplastic nodules in the adrenal gland that develop into adenomas that later develop a malignant phenotype. In support of this, some patients have abnormal adrenal steroid production preceding the development of adrenocortical carcinoma by decades [7, 24]. Cytogenetic analysis suggests that loss of heterozygosity on chromosomes 11p, 13q, or 17p may be important in the pathogenesis [10, 32]. Several recent studies have implicated p53 in the pathogenesis of sporadic adrenocortical carcinoma [17, 21, 27]. This is probably a late event, as mutations in the conserved regions of p53 are detected more frequently in carcinomas than in adenomas.

Classification

Adrenocortical tumors are classified as either functional or nonfunctional. Patients develop symptoms due to

excess amounts of corticosteroid, androgen, estrogen, or mineralocorticoid. Corticosteroid, androgen, and estrogen excesses are much more common than mineralocorticoid excess in adrenocortical carcinoma. Adrenocortical carcinomas are inefficient in steroidogenesis and may not show obvious clinical syndromes of excess, even with large bulky disease. Care must be taken to assay for an abnormal presence of steroid in the blood and urine samples of these patients.

Staging

Adrenocortical carcinoma is staged on the basis of the TNM system [20]. As in the original staging system popularized by MacFarlane [16], stage I disease is tumor measuring less than or equal to 5 cm without local invasion and without nodal or distant metastases. Stage II disease is the same except that the tumor is greater than 5 cm. Stage III disease is associated with local invasion or positive lymph nodes. Stage IV disease is associated with local invasion and positive lymph nodes or distant metastases. In pooled data from multiple institutions, 2% of patients present as stage I; 19%, as stage II; 18%, as stage III; and 61%, as stage IV [12].

Presentation

Adrenocortical carcinoma presents either as a functional tumor or secondary to mass effect. The functional lesions are broadly divided into three groups (corticosteroid, sex hormone, or mineralocorticoid excess) on the basis of the type of hormone they produce. Corticosteroid excess is the most common and more readily recognized presentation of the functional adrenocortical carcinomas. Patients that prersent with corticosteroid excess have the classic stigmata of Cushing's syndrome, including truncal obesity, rounded facies, buffalo hump, stria, hypertension, glucose intolerance, thinning of the skin, and osteoporosis. They sometimes have renal calculi, and if the hormonal excess is high they may have psychiatric problems. Patients that present with sex hormone excess display either excessive virilization (women) or feminization (men). Patients with nonfunctional lesions usually present with a large mass. The associated symptoms are mainly due to size, pressure, and invasion of contiguous structures. Associated symptoms include unexplained fever, anemia, and weight loss in the presence of obesity.

In the Memorial Sloan-Kettering experience, 60% of patients presented with clinically evident functional tumors and 40% presented with clinically nonfunctional tumors [26]. Nonfunctional tumors were defined as those tumors that were seen without signs or symptoms of excess adrenal hormone production, even if excess hormone production was subsequently shown by laboratory analyses. In the group that presented with functional tumors, 50% had Cushing's syndrome, 34% had virilization, 11% had both, 2% had

Table 1 Presentation of adrenocortical carcinoma in MSKCC series[a] [26]

Functional	60%
Cushing's syndrome	50%
Virilization	34%
Cushing's + virilization	11%
Feminization	2%
Hyperaldosteronism	2%
Nonfunctional	40%
Pain	69%
Weight loss + malaise	7%
Hemoturia	7%
Varicocele	3%
Dyspnea	3%
Asymptomatic	10%

[a] $n = 73$

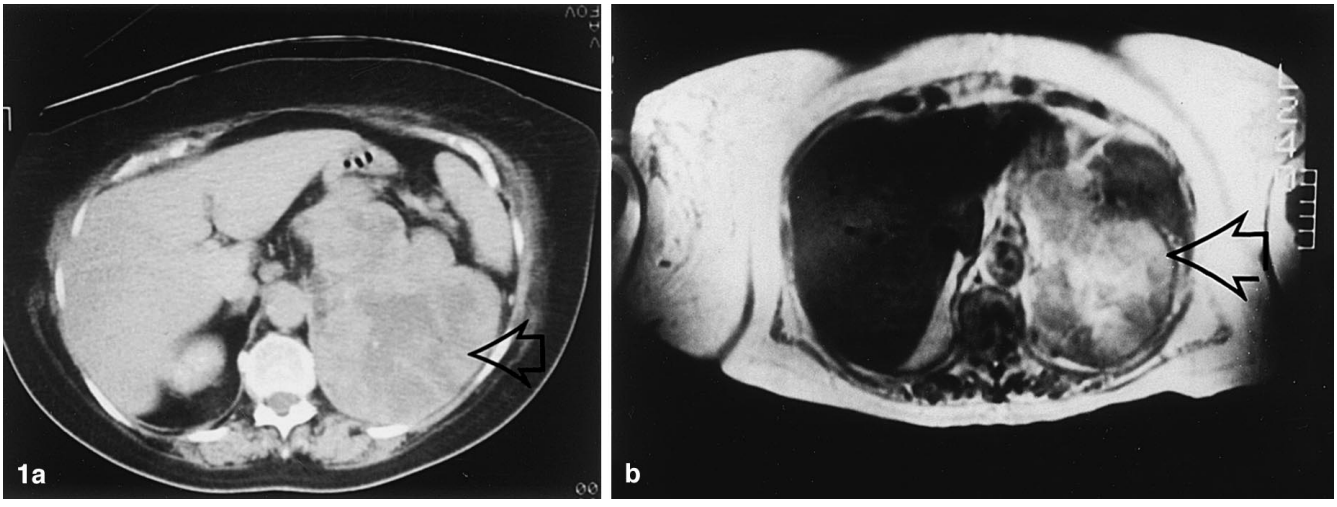

Fig. 1 **a** Patient with a left adrenocortical carcinoma: CT demonstrating an inhomogeneous mass, necrosis, and calcification. **b** Patient with a left adrenocortical carcinoma: MRI demonstrating an inhomogeneous mass and the left crus of the diaphragm separating the aorta from the tumor

Table 2 Factors raising suspicion that an adrenal tumor is an adrenocortical carcinoma [2]

Adrenal Cushing's syndrome
Palpable mass
No suppression with high-dose dexamethasone
Patient younger than 20 years
Increased urinary 17-ketosteroids
Virilization or feminization
Adult with palpable abdominal mass and
CT-positive for adrenal tumor
Increased urinary 17-ketosteroids or 17-OH-corticosteroids
Weight loss or fever

feminization, and 2% had hyperaldosteronism (Table 1). In the group that presented with nonfunctional tumors, 69% had pain, 7% had weight loss and malaise, 7% had hematuria, 3% had varicocele, 3% had dyspnea, and 10% were asymptomatic.

Unfortunately, many of the adrenocortical carcinomas, especially those that are nonfunctional, present as large masses (Fig. 1). In the Memorial Sloan-Kettering experience the mean size of the carcinomas at presentation was 16 cm (range 6–40 cm) and the mean weight was 1190 g (range 320–2600 g) [3]. In a series from France with 156 cases the mean size of the caricinomas at presentation was 12 cm (range 3–30 cm) and the mean weight was 714 g (range 12–4750 g) [11].

Diagnosis

Various factors raise the suspicion that an adrenal tumor is an adrenocortical carcinoma. Patients presenting with Cushing's syndrome and an adrenal mass on imaging studies should be suspected of having adrenocortical carcinoma if they also have a palpable mass, no suppression of serum cortisol on treatment with high-dose dexamethasone (8 mg/day), an age of less than 20 years, or increased urinary 17-ketosteroids. Patients presenting with virilization or feminization syndromes and an adrenal mass on imaging studies should also be suspected of having adrenocortical carcinoma. Patients presenting without signs of steroid excess but with a palpable abdominal mass and an adrenal mass on imaging studies should be suspected if they also have increased urinary 17-ketosteroids or 17-OH-corticosteroids or weight loss and fever (Table 2).

On computerized tomography (CT) scans, adrenocortical carcinomas are typically large, lobulated, and inhomogeneous and have central necrosis and hemorrhage. They may also exhibit irregular enhancement or calcifications, which are usually central [19]. These CT characteristics are nonspecific and may be seen with adenomas, metastatic disease, pheochromocytomas, or granulomatous infections. However, when seen in conjunction with the previously mentioned clinical signs and symptoms, they are suggestive of adrenocortical carcinoma.

Adrenal incidentaloma refers to any adrenal mass discovered serendipitously during an abdominal imaging evaluation. Radiology series show the prevalence of incidentalomas of the adrenal gland to be in the range of 1–2% [14]. In the evaluation of an incidentaloma the possibility of metastatic disease must be considered and excluded. Patients should then be evaluated for potential adrenal function. The presence of a functional lesion is a clear indication for surgical removal. Lesions larger than 5.0 cm should be removed because of the relatively higher incidence of adrenocortical carcinoma in this group.

Extent of disease

Metastatic disease is common in adrenocortical carcinoma. Pooled data from multiple institutions demonstrates that 61% of patients present with stage IV disease. The sites of metastases and the frequencies with which these sites were involved in patients who presented with stage IV disease were reported by Memorial Sloan-Kettering Cancer Center. Metastatic disease to the liver (47%), lung (43%), and lymph nodes (25%) was quite common. Metastasis to other sites occurred less frequently, such as to the bone (15%), omentum/peritoneum (9%), diaphragm (6%), and other miscellaneous sites (skin, brain, palate, bowel, and spleen); (21%) [26].

Once an adrenocortical carcinoma is suspected, CT is the radiology study of choice. Abdominal CT provides information about the tumor's resectability, the patient's renal function, and the presence of metastatic disease to the liver, lymph nodes, or other sites in the peritoneal cavity. CT does not, however, reliably predict invasion of the tumor into the liver, kidney, or inferior vena cava (IVC). Approximation and adherence of the tumor to the liver and kidney are common, but actual invasion occurs much less fequently [2]. Magnetic resonance imaging (MRI) gives information similar to that of CT. Sometimes, planes between the tumor and adjacent organs are better delineated with MRI (Fig. 2). Additionally, MRI has the ability to image the lesion in sagittal and coronal planes (Fig. 3). One advantage of MRI over CT is the ability sometimes to discriminate between the different types of adrenal tumors on the basis of TI- and T2-weighted signal intensities [5, 22]. Adrenocortical carcinomas characteristically have signal intensities that are isointense with the liver on TI-weighted images and are hyperintense on T2-weighted images. Unfortunately, however, there is some overlap in MRI characteristics between certain adrenocortical carcinomas, adrenal metastases, and benign cortical adenomas, which limits the usefulness of MRI. Another advantage of MRI is the ability to image the IVC and determine its involvement by tumor. Lesions that involve the IVC tend to arise from the right side (83%) and tend to be large [9]. Large lesions on the left commonly involve the left renal vein.

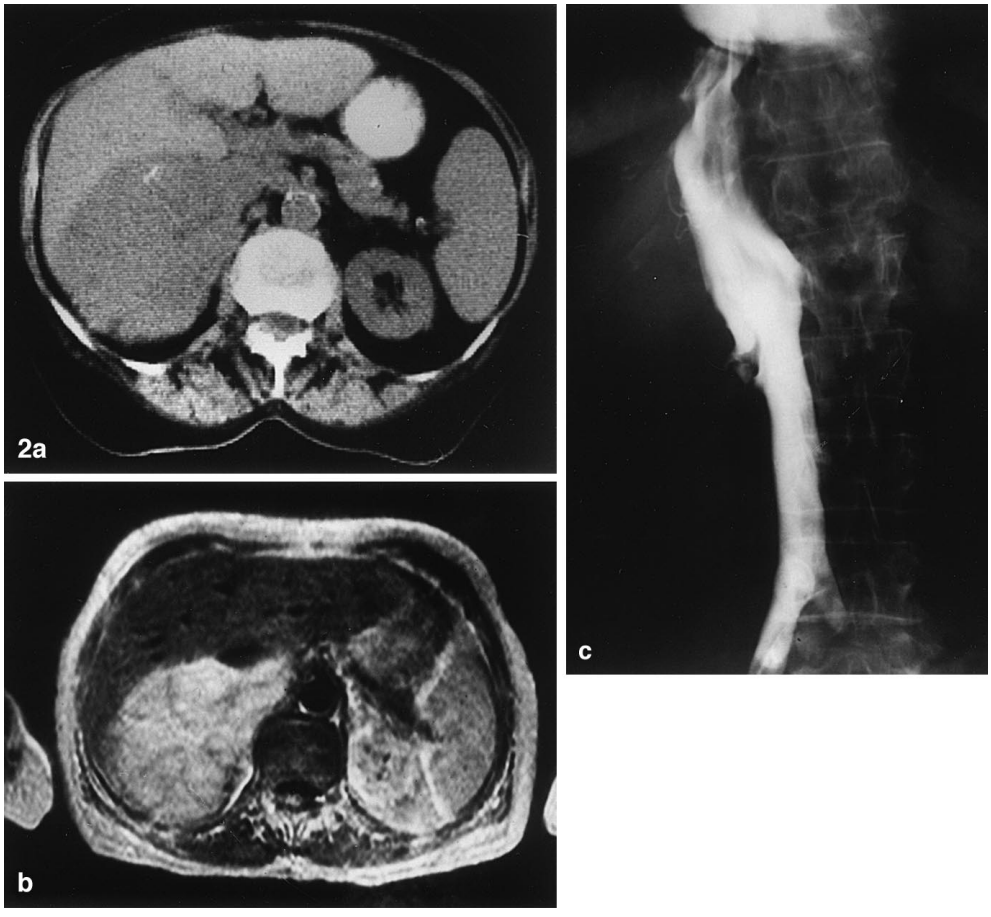

Fig. 2 **a** Patient with a right adrenocortical carcinoma: CT suggesting IVC invasion. **b** Patient with a right adrenocortical carcinoma: MRI demonstrating the IVC to be displaced. **C** Patient with a right adrenocortical carcinoma: venogram confirming no invasion and demonstrating distortion of the IVC with a flow "artifact"

The use of abdominal CT and MRI have supplanted the previous use of venography and aortography. The one potential utility of aortography today is to help differentiate a renal from an adrenal tumor, if that problem should arise. In an extent-of-disease workup, a chest X-ray or CT along with a careful evaluation of the liver by the imaging modality used to evaluate the adrenal gland constitutes sufficient evaluation for metastatic disease. Further extent-of-disease workup should be tailored to the patient's symptoms.

Surgical treatment

The most effective treatment for adrenocortical carcinoma is complete resection. Surgery remains the only potentially curative treatment for this disease. In patients who have biochemically active tumors that secrete corticosteroids and who have suppressed the contralateral gland, careful attention must be given to corticosteroid coverage and replacement. Some argue that

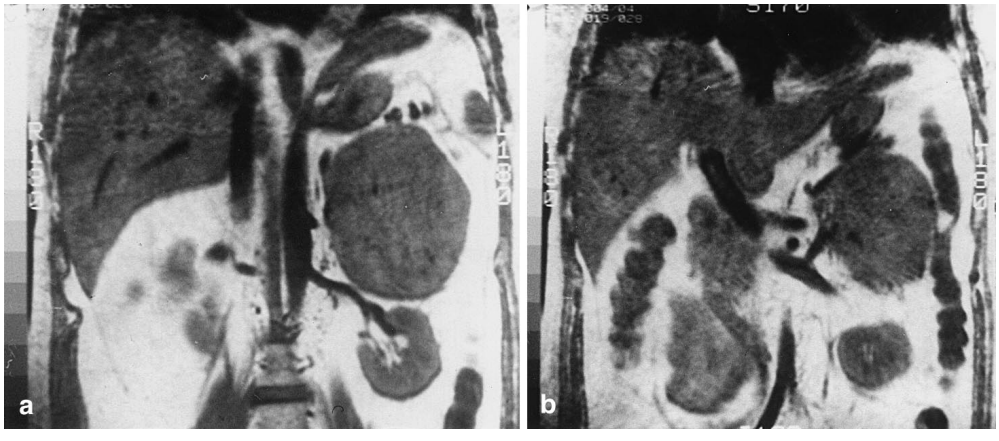

Fig. 3 **a** Patient with a left adrenocortical carcinoma: MRI coronal view. **b** Patient with a left adrenocortical carcinoma: MRI coronal view demonstrating the adrenal vein

perioperative steroids are not required for nonfunctional tumors; however, administration of perioperative steroids is recommended in all cases because virtually all tumors are biochemically active to some degree. The regimen used is similar to the one used in patients who have received long-term exogenous steroids undergoing surgery. These patients should receive 100 mg of hydrocortisone IV on call to the operating room and then every 8 h thereafter. Depending on the degree of adrenal ablation and the recovery of the patient, the dose of hydrocortisone is tapered by 50–100 mg/day until a daily dose of 25–50 mg of hydrocortisone or its oral equivalent is reached. Patients who require long-term steroid maintenance will continue on this daily dose. In patients with Cushing's syndrome it can take upto 22 months before the benign adrenal contralateral gland resumes adequate steroid production [1]. However, most people regain adequate function of the benign contralateral adrenal gland in a much shorter time.

In patients who have had total adrenal ablation and require long-term steroid replacement, mineralocorticoid action should also be replaced. Although corticosteroids have some degree of mineralocorticoid action, in some patients it will not be sufficient. The synthetic adrenocorticoid fludrocortisone acetate is given at an initial dose of 0.1 mg three times a week, which is adjusted according to serum electrolytes and weight gain up to a dose of 0.1 mg/day.

For adrenocortical carcinomas less than 10 cm in size we prefer a bilateral subcostal incision. This affords adequate access to the liver, omentum, peritoneum, and periaortic nodes, which are the common sites of metastasis [2–4, 11, 26, 28, 33]. Invasion by and adherence of the carcinoma into adjacent organs is not unusual, and en-bloc excision of the kidney and regional lymph nodes may be required. However, routine removal of the adjacent kidney is not advocated. Care should be taken not to violate the tumor during the resection to decrease the chance of local recurrence. The right adrenal gland is exposed by mobilization of the hepatic flexure of the colon and performance of a Kocher maneuver to mobilize the duodenum. The inferior portion of the right triangular ligament can then be incised to expose the right adrenal gland. The left adrenal gland can be approached via two techniques. It may be approached inferiorly through the gastrocolic ligament, where the inferior border of the pancreas is mobilized and swept superiorly. This approach will work for smaller lesions. Alternatively, for larger lesions on the left side the left adrenal gland may be approached superiorly by mobilization of the splenic flexure of the colon and then the lateral attachments of the spleen. The spleen, stomach, pancreatic tail, and left colon are then retracted medially en bloc to the superior mesenteric vessels. Limited hepatic resection for metastases and excision of omental or peritoneal implants can be justified in patients who will potentially obtain relief from their symptoms of hormone excess.

For larger lesions (>10 cm) a thoracoabdominal approach is often recommended for better access. This affords safer access and can afford simultaneous removal of ipsilateral pulmonary metastases. The patient is placed in a modified lateral decubitus position. An incision is then made, starting in the midline from the umbilicus and then curving through the costal margin and then on to the superior aspect of the tenth rib. The diaphragm is then incised, leaving a 1- to 2-cm cuff peripherally for reconstruction.

For lesions with intracaval extension, some have advocated the use of cardiac bypass techniques especially for the lesions that extend above the subhepatic vena cava and into the right atrium [9, 13, 18]. This requires a thoracoabdominal incision along with a median sternotomy. Intracaval thrombus from adrenocortical lesions is gelatinous and friable. Often the tumor will spread up the vena cava without direct vascular invasion of the wall. Attempts at extraction or clamping of the vena cava without knowledge of the superior extent of the lesion can result in massive tumor embolus. The tumor emboli can then cause hemodynamic instability via blockage of the pulmonary arteries as in classic pulmonary emboli or they can achieve independent vascularization and growth.

Survival

The prognosis for patients with untreated adrenocortical carcinoma is very poor, with the mean survival

Table 3 Adrenocortical carcinoma: survival rates from reported series

Study	Institution/group	Year	*n*	5-Year survival		
				Overall	Curative resection	Palliative resection
Soreide et al. [28]	Norway	1991	99	16%	62%	0
Pommier and Brennan [26]	MSKCC	1992	73	35%	47%	0
Icard et al. [11]	French Endocrine Surgeons	1992	156	34%	42%	0
Zografos et al. [33]	Roswell Park	1994	53	19%	38%	0
Haak et al. [6]	Holland	1995	96	27%	49%	9%
Crucitti et al. [4]	ACC Italian Registry	1996	129	35%	48%	7%

being only 3 months [16]. In multiple large series the overall 5-year survival in treated patients with adrenocortical carcinoma ranges from 16% to 35% (Table 3). These series consist of patients who were treated with surgery and/or medical therapy most often consisting of 1,1-dichloro-2-[*o*-chlorophenyl]-2-[*p*-chlorophenyl]-ethane (mitotane). In the same series, if the patients' treatment included a complete resection of all disease the 5-year survival ranged from 38% to 62%. If the patients were incompletely resected the 5-year survival ranged from 0 to 9%. These series demonstrate that surgical resection is the primary and only potentially curative treatment for adrenocortical carcinoma. It should be noted that 5-year survival is not equivalent to cure. Most patients surviving at 5 years are alive with disease, and 85% of patients resected for cure will develop recurrence or distant metastases [26].

The studies reviewed in Table 3 have tried to identify clinical factors that are of prognostic significance. Soreide et al. [28] demonstrated that the factors important for prognosis were early stage and curative resection. Pommier and Brennan [26] also demonstrated that these were the factors most important for a good prognosis. In this study the mean survival time for patients with stage I or II disease was 35 months. For patients with stage III disease the mean survival time was 26 months, and for stage IV disease the mean survival time was 9 months. Icard et al. [17] demonstrated that in addition to stage and curative resection, age and type of hormonal secretion influenced survival. In this study the mean survival times of patients with stage I, II, III, and IV tumors were 34, 40, 22, and 8 months, respectively. This translated into 5-year actuarial survival rates of 33% in stage I, 55% in stage II, 24% in stage II, and 0 in stage IV. These authors could also show that the survival of patients younger than 40 years and patients with androgen-secreting tumors was better and that these variables were statistically significant. Zografos et al. [33], much like Soreide et al. [28] and Pommier et al. and Brennan [26], demonstrated that the only two factors of prognostic significance were early stage and curative resection. In this study, median survival times of patients with stage I, II, III, and IV tumors were 46, 84, 8, and 7 months, respectively. The 5-year survival rates were 33%, 57%, 18%, and 7%, respectively. Haak et al. [6] have also concluded that the best chance of survival for a patient with adrenocortical carcinoma is when a complete tumor resection can be performed. Crucitti et al. [4] could not relate age or hormonal activity to survival. They again demonstrated that early stage and curative resection were the two factors of prognostic significance. In this series the actuarial 5-year survival for patients with stage I or II disease was 54%, that for stage III disease was 21%, and that for stage IV disease was 7%.

In addition to identifying clinical factors, many studies have tried to identify pathologic factors of prognostic significance. A recent study at Memorial Sloan-Kettering Cancer Center reviewed 46 patients from their prospective data base who had undergone curative resection for adrenocortical carcinoma [8]. Of the 16 pathologic factors analyzed, tumor size, abnormal mitotic figures, and the presence of intratumoral hemorrhage were independent prognostic factors. Patients presenting with primary tumors measuring ≥12 cm had a worse outcome than those with smaller tumors (5-year survival 22% versus 53%). The presence of >6 abnormal mitotic figures was a negative prognostic feature as compared with the presence of 0–6 abnormal mitotic figures per high-powered field (5-year survival 13% versus 51%). Hemorrhage into the tumor was also a negative prognostic factor as compared with lesions without intratumoral hemorrhage (5-year survival 22% versus 53%). In this study, patients with none of these risk factors demonstrated a favorable 5-year survival of 83%. No patient with all three pathologic risk factors was alive at 5 years despite complete resection. Patients with 1 or 2 of the pathologic risk factors had intermediate 5-year survival values of 42% and 33%, respectively.

Medical therapy

The chemotherapeutic agent most often used to treat adrenocortical carcinoma is mitotane (Table 4). This agent was developed as an insecticide and is taken up by the adrenal cortex and causes necrosis of the adrenal cortex. Its specific cytotoxic effect on the adrenal cortex has led to its use in adrenocortical carcinoma. It is used in both primary therapy and adjuvant therapy settings. Venkatesh et al. [30] reported on 72 patients treated with mitotane and found an objective partial response rate of 29%. However, the 2-year survival of this group of patients was only 13%. These authors concluded that early diagnosis and complete surgical excision offered the best prospects for long-

Table 4 Adrenocortical carcinoma: response to mitotane therapy (*CR* Complete objective response, *PR* partial objective response)

Study	Institution /group	Year	*n*	Response	Comment
Venkatesh et al. [30]	MD Anderson	1989	72	29%	PRs only
Luton et al. [15]	France	1990	59	14%	PRs only
Pommier et al. [26]	MSKCC	1992	29	24%	PRs only
Wooten and King [31]	English Literature Review	1993	551	35%	PRs + CRs
Haak et al. [6]	Holland	1995	55	27%	PRs + CRs

term survival and that the efficacy of adjuvant mitotane needed to be evaluated further. Luton et al. [15] reported on 59 patients who received mitotane and found partial tumor regression in 14%. They did not find a significant increase in survival in patients treated with mitotane. They concluded that mitotane therapy might offer transient benefits, particularly in controlling endocrine symptoms. Pommier and Brennan [26] reported on 29 patients who received mitotane and found partial objective responses in 7 of these (24%). They did not find a significant increase in survival in patients treated with mitotane. They concluded that the value of adjuvant therapy after complete resection remained unproven. Wooten and King [31] reviewed the English literature from 1952 to 1992 for reports of patients with adrenocortical carcinoma. They paid particular attention to the use of mitotane and patient outcomes. They found 64 reports (551 patients) that had patients treated with mitotane. Of these, 194 (35%) patients had at least a partial response to mitotane. These authors pointed out, however, that the definition of partial response was varied and broad. Haak et al. [6] reported on 55 patients who received mitotane and had evaluable tumors because they were not operated upon but only underwent a subtotal resection or had tumor recurrence. They reported that 7 (13%) of these patients had partial objective responses and 8 (15%) had complete objective responses when subsequently treated with mitotane. They found increased survival times in patients treated with mitotane if serum levels were continuously kept above 14 mg/l. This difference in survival was statistically significant. In patients with serum levels kept above 14 mg/l, objective responses were found in 15 of the 27 (55%) evaluable patients. These authors concluded that mitotane treatment for patients with inoperable, recurrent, and/or metastatic adrenocortical carcinoma was effective if serum levels of the drug were maintained above 14 mg/l.

Significant toxicity is associated with mitotane therapy [25]. Almost all patients experience gastrointestinal symptoms consisting of nausea and anorexia. Neuromuscular toxicity, including lethargy, dizziness, somnolence, and depression, occur in 40–60% of patients. Many patients cannot carry out normal work or leisure activities because of the side effects. Adrenal insufficiency secondary to mitotane's toxicity against normal adrenal tissue is almost universal in patients taking the drug. Steroid replacement as outlined above should routinely be used in patients treated with mitotane. Corticosteroid replacement, therapy should not be tapered until the patient has been off mitotane for at least 1 month [2]. In addition to corticosteroid replacement, care must be taken to replace the mineralocorticoid function of the adrenal gland during mitotane therapy.

Many other chemotherapeutic agents have been evaluated for efficacy against adrenocortical carcinoma. Chemotherapy regimens besides mitotane have not been as effective against adrenocortical carcinoma [20]. Cisplatin and etoposide show some activity in this disease and are sometimes used in patients who have failed mitotane therapy. Suramin has also shown some activity in this disease and has been used in the setting of metastatic disease. It must be viewed as an agent with low efficacy and high toxicity.

Several medications (in addition to mitotane) are used in the treatment of symptoms caused by hormonal excess. To control symptoms of glucocorticoid excess, ketoconazole, aminoglutethimide, and metyrapone have been used. Ketoconazole is an imidazole-derivative antifungal agent. It blocks enzymes in the biosynthetic pathway of corticosteroid production (11-beta-hydroxylase and others). Aminoglutethimide blocks adrenal steroidogenesis (conversion of cholesterol to delta-5-pregnenolone) and is useful in inhibiting cortisol synthesis. Metyrapone inhibits cortisol production by inhibiting 11-beta-hydroxylase, much like ketoconazole. However, it also blocks the synthesis of aldosterone, and its prolonged use can result in increased serum levels of aldosterone precursors, which are also potent mineralocorticoids. This can result in hypertension and hyperkalemia. To control the symptoms of mineralocorticoid excess, spironolactone has been used. Spironolactone is a competitive inhibitor for the aldosterone receptor. It will usually correct hypokalemia but is frequently inadequate at controlling hypertension.

Radiotherapy

Radiation therapy is of very limited benefit in adrenocortical carcinoma. It does not prolong survival, but it does appear to provide significant palliation for pain from bone metastases [3, 20, 23].

Reoperative treatment

Even for patients who undergo complete resection, recurrent and metastatic disease are extremely common. At Memorial Sloan-Kettering Cancer Center the recurrence rate for patients who underwent complete resection was 85% [26]. The only effective treatment for recurrent adrenocortical carcinoma is reoperation. Resection of recurrent and metastatic disease prolongs disease-free survival and provides excellent palliation in cases associated with symptomatic steroid production. Cohn et al. [3] reported on 9 patients who underwent resection of abdominal recurrences and/or pulmonary metastases. The mean survival of this group of patients was 3.5 years, which compared favorably with the mean survival of 3.1 years recorded for all patients in that series. This was accomplished with no mortality and minimal morbidity. Pommier and Brennan [26] reported on 26 patients who underwent resection for recurrent or metastatic disease after complete resection. These 26 patients underwent 51 reoperations, which included thoracotomy, liver resection, vertebral body resection,

and craniotomy. Of these reoperations, 41 (82%) were complete resections, and the operative mortality and morbidity were 0 and 2%, respectively. The mean survival time of patients who recurred and were treated with reoperation was 56 months, whereas those treated medically had a mean survival time of 19 months. Icard et al. [11] reported on 22 patients who underwent reoperation for local recurrence. The 5-year actuarial survival was 27% when calculated from the time of the original operation and 16% when calculated from the time of reoperation. When the reoperation was curative the 5-year actuarial survival calculated from the time of reoperation was 28%. Crucitti et al. [4] reported on 11 patients who underwent reoperation for recurrent disease. They reported no operative mortality or morbidity from these reoperations. In all, 10 of the patients underwent tumor debulking, 3 underwent nephrectomy, 1 underwent splenectomy, and 1 underwent liver metasectomy. The mean survival in the reoperated patients was 42 months. In this series the patients with recurrence who did not undergo reoperation had a mean survival time of 16 months. It is clear that patients with recurrent or metastatic disease should undergo reoperation if they have potentially resectable disease and can withstand an operation.

Follow-up

Recurrence and metastatic disease is common in adrenocortical carcinoma. Of patients undergoing complete resection, 85% will develop recurrence or metastatic disease [26]. Follow-up patterns are dependent on the philosophy directed at recurrence. As most authors would resect isolated local recurrence of resectable lung metastases, chest X-ray and abdominal CT form the mainstay of postresection surveillance. Patients in whom dehydorepiandrosterone (DHEAS) is elevated can be followed with this serum marker. Patients who had tumors that produced elevated levels of urinary corticosteroids should have their urine checked every 3–6 months. A rise in urinary steroid levels often signals a recurrence long before symptoms, physical findings, or radiologic examination. Where an aggressive approach is contemplated (young patient, initial early stage, complete resection), careful histories and physical examinations as well as CT of the abdomen and chest X-ray should be performed every 3 months for the first 2 years and then every 6 months thereafter. Follow-up should be continued indefinitely, as recurrences can occur very late.

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