ORIGINAL ARTICLE

Adjuvant Mitotane Treatment for Adrenocortical Carcinoma

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ABSTRACT

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BACKGROUND

Adrenocortical carcinoma is a rare neoplasm characterized by a high risk of recurrence after radical resection. Whether the use of mitotane is beneficial as an adjuvant treatment has been controversial. Our aim was to evaluate the efficacy of adjuvant mitotane in prolonging recurrence-free survival.

METHODS

We performed a retrospective analysis involving 177 patients with adrenocortical cancer who had undergone radical surgery at 8 centers in Italy and 47 centers in Germany between 1985 and 2005. Adjuvant mitotane was administered to 47 Italian patients after radical surgery (mitotane group), whereas 55 Italian patients and 75 German patients (control groups 1 and 2, respectively) did not receive adjuvant treatment after surgery.

RESULTS

Baseline features in the mitotane group and the control group from Italy were similar; the German patients were significantly older (P=0.03) and had more stage I or II adrenocortical carcinomas (P=0.02) than did patients in the mitotane group. Recurrence-free survival was significantly prolonged in the mitotane group, as compared with the two control groups (median recurrence-free survival, 42 months, as compared with 10 months in control group 1 and 25 months in control group 2). Hazard ratios for recurrence were 2.91 (95% confidence interval [CI], 1.77 to 4.78; P<0.001) and 1.97 (95% CI, 1.21 to 3.20; P=0.005), respectively. Multivariate analysis indicated that mitotane treatment had a significant advantage for recurrence-free survival. Adverse events associated with mitotane were mainly of grade 1 or 2, but temporary dose reduction was needed in 13% of patients.

CONCLUSIONS

Adjuvant mitotane may prolong recurrence-free survival in patients with radically resected adrenocortical carcinoma.

ADRENOCORTICAL CARCINOMA IS A RARE neoplasm characterized by a dismal prognosis, with only 16 to 38% of patients surviving for more than 5 years after diagnosis.[1-3] Although a majority of patients have resectable disease at presentation,[4-6] as many as 75 to 85% have a relapse after radical resection.[7,8] This high recurrence rate has prompted investigators to consider the use of adjuvant therapy,[1-3,9] and mitotane (a synthetic derivative of the insecticide dichlorodiphenyltrichloroethane [DDT]) has been widely used for this purpose.[10-21] However, available studies do not provide data as to whether adjuvant mitotane is efficacious, mainly because of the low statistical power of the studies.

We reviewed the outcome of patients with adrenocortical carcinoma who had undergone radical surgery at tertiary referral centers in Italy from 1985 through 2003. During this period, adjuvant mitotane treatment was routinely used in some centers but not in others, providing an opportunity to compare two contemporary groups of patients. To control further for potential biases, we included a second independent control group for comparison with mitotane-treated patients in our analysis, a cohort of German patients who were treated with surgery only. The primary aim of the study was to evaluate the efficacy of adjuvant mitotane in prolonging recurrence-free survival; secondary aims were assessments of overall survival and adverse events.

METHODS

ITALIAN PATIENTS

We performed a retrospective analysis among patients with adrenocortical carcinoma who had undergone radical surgery between January 1985 and December 2003 at eight tertiary referral centers in Italy. All patients who had undergone radical resections were included in the study. Follow-up for this study was closed in December 2004.

Patients had to meet the following inclusion criteria: an age of 18 years or older and the availability of preoperative and postoperative computed tomographic (CT) or magnetic resonance imaging (MRI) scans. Exclusion criteria were macroscopically incomplete resection, incomplete tumor staging, concomitant cancers within the previous 5 years, clinically significant concomitant disease, and adjuvant therapies other than mitotane (chemotherapy or radiotherapy) after surgery.

Of 131 patients identified, 102 met all entry criteria. Of those, 29 patients were excluded: 21 had undergone an incomplete resection, 3 had other concomitant tumors, 4 had undergone other adjuvant therapies, and 1 had heart failure.

All data were obtained by reviewing patients' histories, discharge summaries, medical records, and source documents. Data were retrieved by trained medical personnel using specifically tailored data forms. We collected data on the date of diagnosis, the date of surgery, the pathology report, the tumor stage at diagnosis, the hormonal workup, details concerning mitotane treatment (treatment duration and regimen, side effects, and reasons for discontinuation), the date of recurrence, and either the date and cause of death or the date of the last follow-up visit. The institutional ethics committee at each clinical center approved the study. All patients provided written informed consent.

Complete resection was defined as no evidence of macroscopic residual disease on the basis of surgical reports, histopathological analysis, and postoperative imaging. All histologic diagnoses were confirmed by experienced pathologists. In 89% of the patients, two expert pathologists who were unaware of study-group assignments reevaluated the histologic analysis according to the Weiss criteria (nuclear atypia, atypical mitoses, frequent mitoses, small percentage of clear cells, diffuse architecture, necrosis, and the invasion of venous, sinusoidal, or capsular structures).[22,23] Follow-up visits, which included imaging of the chest and abdomen, were performed every 6 months until either disease progression occurred or the study period ended.

Tumor staging at diagnosis was based on imaging studies and was corroborated by the findings during surgery. Staging was reported according to the McFarlane–Sullivan criteria: stage I, a tumor diameter of 5 cm or less; stage II, a tumor diameter of more than 5 cm; stage III, tumor infiltration of neighboring structures or positive lymph nodes; and stage IV, infiltration of neighboring structures and positive lymph nodes or distant metastases.[24,25] Disease recurrence was defined as radiologic evidence of a new lesion during follow-up.

Adjuvant mitotane (Lysodren, Bristol-Myers Squibb) was routinely recommended at four of the Italian centers, whereas patients were followed without treatment at the other four centers. Mito-

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tane-related adverse events were graded with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events.[26]

GERMAN PATIENTS

A second control group was derived from the German Adrenocortical Carcinoma Registry, which contained data for 345 patients at the time of analysis (August 2006). Clinical data for these patients were collected by trained medical personnel using structured evaluation forms containing comprehensive information on diagnostic procedures, surgical outcomes, and follow-up similar to those used to evaluate the Italian study population (further details are available at www.nebennierenkarzinom. de). The German Adrenocortical Carcinoma Registry was approved by the ethics committee at the University of Würzburg, and patients gave written informed consent.

Follow-up data were available for 333 patients. Of those, 181 patients who were at least 18 years of age presented without distant metastases, and 148 of these patients had undergone radical surgery with curative intent. Detailed surgical reports indicated no residual disease in 111 patients. Thirty-six patients were excluded because they had undergone adjuvant therapies, including mitotane (22 patients; median duration of treatment, 7.5 months), radiotherapy (7), cytotoxic drugs (1), or combinations of these treatments (6). The remaining 75 patients met the inclusion and exclusion criteria of the Italian observation group. They had undergone radical resection between 1985 and 2005 in 47 centers throughout Germany. The histologic diagnosis for each patient was made by the local pathologist. In 73% of patients, tumor material was made available to the study pathologist, who confirmed the diagnosis in all cases. Information on the functional status of adrenocortical carcinoma (whether the tumor was hormone-secreting) was available for 50 patients.

OUTCOMES

The primary aim of our study was to compare recurrence-free survival in patients who received adjuvant mitotane therapy after radical resection with that of patients who did not receive adjuvant therapy. Secondary outcome measures were overall survival and adverse events associated with mitotane therapy. Recurrence-free survival was measured from the date of surgery to the date of recurrence; for patients who did not have a relapse, the data

were censored at the date of the last follow-up visit. Overall survival was measured from the date of surgery to the date of death, and the data were censored at the date of the last follow-up visit.

STATISTICAL ANALYSIS

All statistical analyses were performed with Statistica software (StatSoft). Rates and proportions were calculated for categorical data and medians and ranges for continuous data. Differences in continuous variables were analyzed by means of the two-tailed Mann–Whitney U test. For categorical variables, differences were analyzed by means of the chi-square test. Survival curves were computed according to the Kaplan–Meier method and were compared by means of the log-rank test. A Cox proportional-hazards regression analysis was used to assess in univariate and multivariate analyses the predictive role of the treatment administered and of clinical and pathological variables on disease recurrence and overall survival. The likelihood ratio was used to assess the significance of covariates included in each model. Heterogeneity in the effect of adjuvant treatment in subgroups of patients was evaluated with the use of standard tests for interaction. Missing data were dealt with by excluding patients from particular analyses if their files did not contain data for the required variables. All reported P values are two-sided. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

PATIENTS

The characteristics of patients according to group are provided in Table 1. The groups of Italian patients (the mitotane group and control group 1) were evenly distributed with respect to age and stage of disease, whereas the German patients (control group 2) were significantly older than the patients in the mitotane group (P=0.03). Patients with stage IV adrenocortical carcinoma had infiltration of adjacent organs; none had distant metastases. A higher proportion of men was present in control group 1 than in the mitotane group (P=0.05), whereas sex distribution in control group 2 did not differ significantly from that in the mitotane group. The mitotane group and control group 1 were evenly distributed with respect to tumor stage, whereas the proportion of adrenocortical carcinomas of stage I or II was higher

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Mitotane Group (N = 47)	Control Group 1 (N = 55)	P Value	Control Group 2 (N = 75)	P Value
Age — yr			0.30		0.03
Median	42	44		47	
Range	18–67	21–73		18–83	
Sex — no. (%)			0.05		0.1
Male	11 (23.4)	23 (41.8)		27 (36.0)	
Female	36 (76.6)	32 (58.2)		48 (64.0)	
Tumor stage — no. (%)			0.90		0.02†
I	3 (6.4)	4 (7.3)		9 (12.0)	
II	27 (57.4)	31 (56.4)		54 (72.0)	
III	11 (23.4)	15 (27.3)		11 (14.7)	
IV	6 (12.8)	5 (9.1)		1 (1.3)	
Tumor size — cm			0.40		0.50
Median	10.5	10.0		10.0	
Range	5.0–22.0	4.0–22.0		3.0–28.0	
Functional status of tumor — no. (%)					
Total no. of patients evaluated	47	55		50	
Secreting tumor	24 (51.1)	22 (40.0)	0.30	30 (60.0)	0.40
Glucocorticoids with or without androgens	22 (46.8)	15 (27.3)		25 (50.0)	
Androgens	2 (4.3)	5 (9.1)		4 (8.0)	
Aldosterone	0	1 (1.8)		1 (2.0)	
Estradiol	0	1 (1.8)		0	
Nonsecreting tumor	23 (48.9)	33 (60.0)		20 (40.0)	
Weiss score‡					
Total no. of patients evaluated	45	46		43	
Median (range)	6 (3–9)	6 (3–8)	0.20	5 (2–9)	0.09

* All P values are for comparisons between each control group and the mitotane group. Percentages may not total 100 because of rounding.
† The P value refers to the overall tumor-stage distribution.
‡ The Weiss score ranges from 0 to 9, with a score higher than 2 indicating the presence of adrenal cancer.
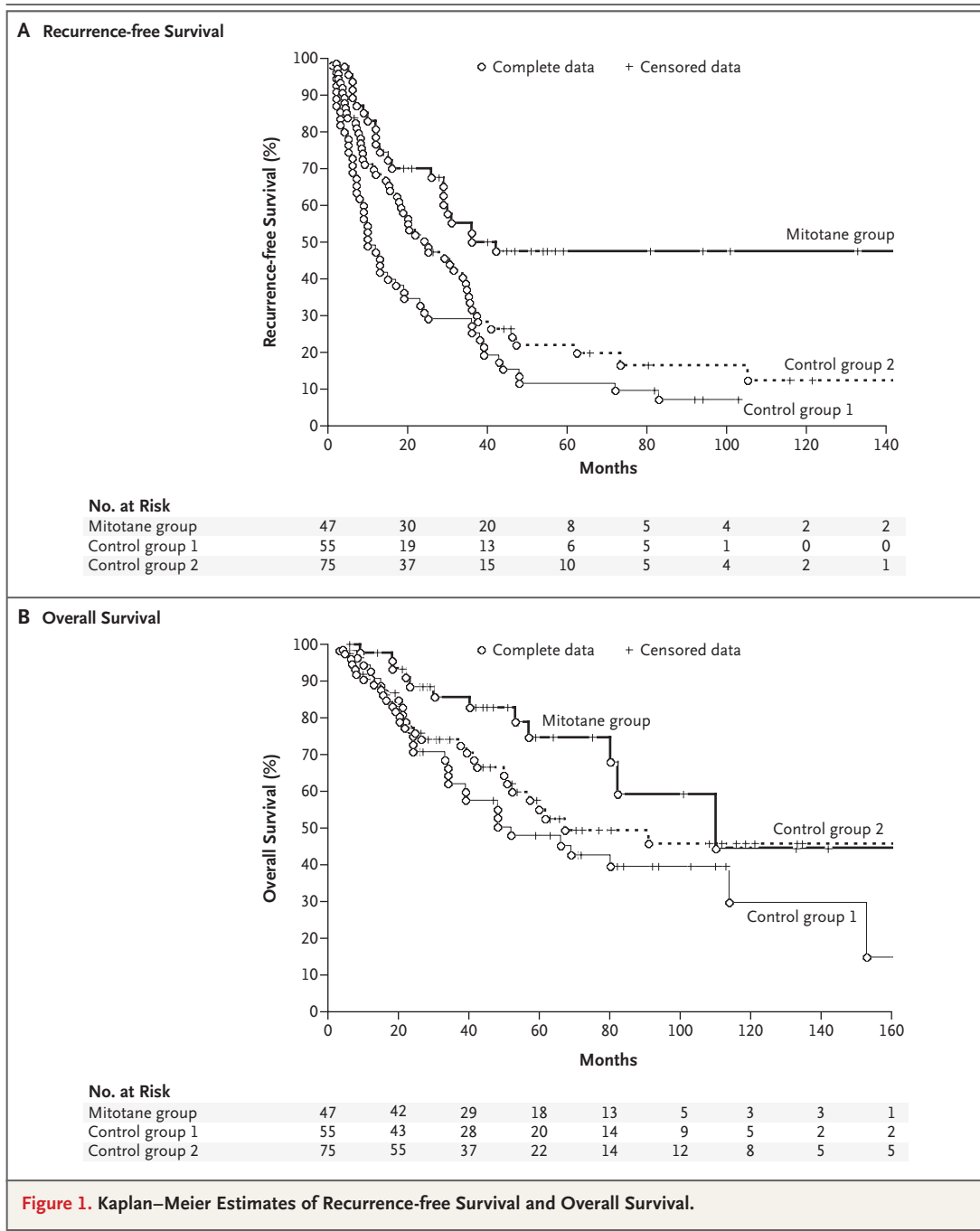
in control group 2 than in the mitotane group (P=0.02). Of the 152 patients who could be evaluated, 50% had secreting tumors, with no major difference between groups. The median follow-up period after surgery was 56.7 months (range, 12 to 164) in the mitotane group, 67.6 months (range, 12 to 161) in control group 1, and 43.0 months (range, 9 to 230) in control group 2.

OUTCOME RESULTS

Recurrence was documented in 23 patients in the mitotane group (48.9%), 50 in control group 1 (90.9%), and 55 in control group 2 (73.3%). Mito-

tane treatment was associated with longer recurrence-free survival, as compared with either control group (Fig. 1A). The median recurrence-free survival was 42 months in the mitotane group, 10 months in control group 1 (P<0.001), and 25 months in control group 2 (P=0.005), according to the log-rank test.

Death from adrenocortical cancer was reported for 12 patients in the mitotane group (25.5%), 30 in control group 1 (54.5%), and 31 in control group 2 (41.3%). Three patients in the mitotane group and one in control group 1 died from other causes and had no evidence of recurrence. Me-

A Recurrence-free Survival

No. at Risk

Mitotane group	47	30	20	8	5	4	2	2
Control group 1	55	19	13	6	5	1	0	0
Control group 2	75	37	15	10	5	4	2	1

B Overall Survival

No. at Risk

Mitotane group	47	42	29	18	13	5	3	3	1
Control group 1	55	43	28	20	14	9	5	2	2
Control group 2	75	55	37	22	14	12	8	5	5

Figure 1. Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival.

dian overall survival was 110 months in the mitotane group, as compared with 52 months in control group 1 (P=0.01) and 67 months in control group 2 (P=0.10), according to the log-rank test (Fig. 1B).

Among patients in all the groups, recurrences were managed with surgery (56.2%), mitotane (70.3%), cytotoxic chemotherapy (42.2%), or other therapies (7.5%); these approaches were often used in combination. Six of 128 patients with recurrence did not receive any specific treatment.

To adjust for imbalances in the distribution of potential prognostic factors between comparisons of recurrence-free survival and overall survival, two multivariate Cox models were fitted to the data, in which age, sex, and tumor stage were included

as covariates together with treatment group (mitotane group vs. control group 1 vs. control group 2). Since data on tumor secretory activity and Weiss score were not available for all patients in control group 2, two further multivariate models that included these two variables were fitted on data for the Italian patients. However, since secretory activity and the Weiss score were not found to be associated with either recurrence-free or overall survival and since the inclusion of these variables did not modify hazard-ratio estimates, only the results of the multivariate analyses of the full data set of 177 patients are presented (Tables 2 and 3). In the univariate analysis, only age was significantly associated with recurrence-free survival and overall survival (P<0.001). After adjustments for age, sex, and tumor stage, both the Italian and the German control groups showed a higher risk of both recurrence (hazard ratio, 3.79; 95% confidence interval [CI], 2.27 to 6.32; and hazard ratio, 2.93; 95% CI, 1.74 to 4.94, respectively) and death (hazard ratio, 2.47; 95% CI, 1.26 to 4.85; and hazard ratio, 1.96; 95% CI, 1.00 to 3.87, respectively) than did the mitotane group. No heterogeneity in the hazard ratios was observed across subgroups of patients identified by the prognostic factors included in the model (all P values for interaction, >0.2).

MITOTANE DOSE AND ADVERSE EVENTS

In the mitotane group, 20 patients received 3 to 5 g daily, and 27 patients received 1 to 3 g daily. The median duration of treatment was 29 months (range, 6 to 164) with no significant difference between the two regimens; 21 patients were treated for 4 years or more.

The adverse events associated with mitotane therapy are listed in Table 4. Grade 3 gastrointestinal events were observed in 15% of patients and neurologic grade 3 events in 20% of patients who received the higher-dose regimen; neither of these problems was seen in patients receiving the lower-dose regimen. Temporary discontinuation or dose reduction was necessary in four patients receiving higher doses of mitotane and in two patients receiving lower doses.

DISCUSSION

Our study suggests a benefit associated with the use of adjuvant mitotane therapy after radical re-

Table 2. Predictive Factors for Recurrence-free Survival, According to Univariate and Multivariate Analyses.

Variable	Univariate Analysis			Multivariate Analysis*		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Age†	0.98	0.96–0.99	<0.001	0.97	0.96–0.98	<0.001
Sex‡	1.20	0.83–1.72	0.33	1.08	0.74–1.58	0.67
Tumor stage			0.27			0.03
I	1			1		
II	1.91	0.92–3.95		2.10	1.00–4.28	
III	2.14	0.98–4.71		2.45	1.10–5.41	
IV	2.22	0.85–5.80		4.34	1.61–11.67	
Secreting tumor§	1.29	0.87–1.90	0.20			
Weiss score¶	0.96	0.61–1.50	0.85			
Study group						
Mitotane group	1		<0.001	1		<0.001
Control group 1	2.91	1.77–4.78		3.79	2.27–6.32	
Control group 2	1.97	1.21–3.20		2.93	1.74–4.94	

* The model for the multivariate analysis included age (as a continuous variable), sex (as a dichotomized variable), and tumor stage (in four strata) as covariates. No significant interactions between treatment group and age, sex, or tumor stage were observed, but the low power of these analyses must be considered, given the small number of events.
† The hazard ratio is for each additional year of age.
‡ Female sex was the reference category.
§ Nonsecreting adrenocortical carcinoma was the reference category.
¶ A Weiss score of 6 (median value) or less was the reference category.

section of adrenocortical carcinoma. As compared with patients treated with mitotane, patients in both the Italian and the German control groups appeared to have a significantly increased risk of recurrence (by factors of 3 and 2, respectively). The apparent benefit of mitotane therapy was even more marked when multivariate analyses were used. Similarly, overall survival appeared to be superior in patients receiving adjuvant mitotane.

Our study had certain limitations, since it was not a randomized trial. Indeed, potential problems such as selection bias, diagnostic bias, stage migration, and bias in follow-up or ascertainment of outcome in observational retrospective series are well recognized. To reduce selection bias in the Italian centers, we included all consecutive eligible patients in the study group of the given center (in the mitotane group and control group 1) on the basis of the treatment policy of that center, as established by specific management algorithms and not dependent on the characteristics of patients. Control group 2 was derived from a large nationwide registry of patients with adrenocortical carcinoma, and the 75 patients in this group were extracted from a subgroup of 333 patients for whom follow-up data were available. Thus, it is reason-

able to assume that control group 2 was representative of all patients with resected adrenocortical carcinoma in Germany during the study period. Furthermore, no patients were excluded on the basis of treatment adherence or outcome.

The possibility that patients with different unmeasured characteristics were unevenly distributed between the Italian groups or that surgery may have been more complete in some centers than in others cannot be completely excluded. It should be noted, however, that the only difference in the distribution of known or potential prognostic factors between the two groups of Italian patients was the higher proportion of male patients in control group 1, which is unlikely to have affected the results, since the sex of patients was not an independent predictor of survival. Patients in the German control group, in contrast, were older, and more had early-stage cancers than did patients in the mitotane group. However, these differences would have predicted a better prognosis in the German control group than in the mitotane group. Accordingly, when adjustments were made for the differences in the distribution of these factors with the use of multivariate analyses, larger hazard-ratio estimates were obtained, reinforcing the possibil-

Table 3. Prognostic Factors for Overall Survival, According to Univariate and Multivariate Analyses.

Variable	Univariate Analysis			Multivariate Analysis*		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Age†	0.98	0.96–1.00	0.05	0.98	0.96–1.00	0.02
Sex‡	0.90	0.55–1.47	0.68	0.78	0.46–1.33	0.36
Tumor stage			0.26			0.29
I	1			1		
II	3.81	0.93–15.68		3.68	0.90–15.23	
III	4.47	1.03–19.86		4.22	0.97–18.43	
IV	3.54	0.65–19.85		4.40	0.79–24.58	
Secreting tumor§	1.32	0.78–2.24	0.30			
Weiss score¶	1.04	0.57–1.89	0.89			
Study group						
Mitotane group	1		0.05	1		0.03
Control group 1	2.28	1.17–4.46		2.47	1.26–4.85	
Control group 2	1.73	0.89–3.39		1.96	1.00–3.87	

* The model for the multivariate analysis included age (as a continuous variable), sex (as a dichotomized variable), and tumor stage (in four strata) as covariates. No significant interactions between treatment group and age, sex, or tumor stage were observed, but the low power of these analyses must be considered, given the small number of events.
† The hazard ratio is for each additional year of age.
‡ Female sex was the reference category.
§ Nonsecreting adrenocortical carcinoma was the reference category.
¶ A Weiss score of 6 or less (median value) was the reference category.

ity that the use of mitotane was associated with a true prognostic improvement. Differences in histologic classification among the three groups were unlikely, since data from most of the patients were reviewed by expert pathologists who all used the same classification criteria.[22,23] Diagnostic and staging protocols were similar in all centers, and patients in the three groups underwent surgery during the same period. Finally, follow-up was sufficiently complete in the three groups, with only six patients lost to follow-up. Thus, as far as can be stated in a retrospective study, major biases appear to have been minimal.

Our study compared adjuvant mitotane therapy with no adjuvant therapy in two groups of similar patients, whereas historical controls or no controls were used in previous studies.[5,7,10-20] Strengths of our study include the large number of patients, the long duration of follow-up, the use of intention-to-treat analysis, and the inclusion of two independent, concomitant groups of patients who received no adjuvant therapy after their initial surgery. Notwithstanding the retrospective nature of this study, which warrants caution in the interpretation of its results, the study provides important evidence for the efficacy of adjuvant treatment with mitotane after radical resection of adrenocortical carcinoma.

Adrenocortical carcinoma is a heterogeneous disease characterized by a generally dismal prognosis, with few patients having either long recurrence-free intervals or overall survival.[3,8,27,28] This observation points to the importance of identifying prognostic factors. In our study, tumor stage did not appear to have significant prognostic value. However, more advanced stages were associated with increased risk of either disease recurrence or death, and the failure to attain statistical significance for overall survival may be due to the low number of patients with stage I tumors. In addition, the tumor stage may affect prognosis primarily as it affects the feasibility of radical surgery, which was an inclusion criterion of the study. It is known that patients with adrenocortical carcinoma have an extremely poor prognosis when surgical removal of the tumor is not feasible.[2,4-8,15,28]

Age was the only consistent prognostic factor associated with an improved outcome. However, the bulk of previous evidence suggests that age does not play a major role in prognosis.[8,28-30] Similarly, the majority of studies have reported no correlation between sex and survival,[5,7,13,28,30] and

Table 4. Adverse Events.*				
Event	Grade			
	1	2	3	4
	no. of patients			
Hematologic symptom				
Leukopenia	4	2	0	0
Constitutional or gastrointestinal symptom				
Asthenia or fatigue	17	6	1	0
Diarrhea	8	5	0	0
Nausea or vomiting	13	10	3	0
Anorexia	20	7	0	0
Hepatic symptom				
Elevated γ-glutamyltransferase	23	10	7	0
Elevated aspartate or alanine aminotransferase	19	4	0	0
Neurologic symptom				
Confusion	4	5	2	0
Ataxia	2	1	4	0
Vertigo	4	5	4	0
Other symptom				
Blurred vision	0	1	0	0
Gynecomastia	3	1	0	0

* Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events. Owing to the adrenolytic action of mitotane, all patients received prophylactic glucocorticoid replacement therapy. Therefore, detailed monitoring of mitotane-induced adrenal insufficiency was not performed. Because of the retrospective nature of the study, underreporting of low-grade side effects must be considered a possibility.

there is only limited evidence that the Weiss score[23] is predictive of long-term outcome.[3,31,32] The functional status of the tumor is also usually not related to prognosis,[1,7,11-13,15,28,30] although in advanced disease, hypercortisolism may contribute to an unfavorable outcome.[33]

Adjuvant mitotane treatment was associated with some adverse events, which may be considered acceptable, given the disease. However, because of the retrospective nature of our study, underreporting of adverse events cannot be fully excluded. Adverse events were manageable, though a temporary reduction of the mitotane dose was necessary in some patients. Mitotane was not terminated because of adverse events in any of the patients.

In summary, our study indicates that adjuvant treatment with mitotane can be administered with beneficial effects on outcome in patients with adrenocortical carcinoma. We believe that our retrospective analysis should renew interest in adju-

vant therapy as a key issue in the treatment of this disease. In the future, prospective, randomized trials will be needed to confirm that adjuvant mitotane treatment is sufficiently effective to be considered as the standard of care after complete resection of adrenocortical carcinoma.

APPENDIX

The following investigators contributed two or more patients to the German control group: H. Willenberg, P. Goretzki (University Hospital, Düsseldorf); M. Rothmund, P. Langer (University Hospital, Marburg); M. Quinkler, W. Oelkers (University Hospital Charité, Berlin); H. Denecke (Leopoldina Hospital, Schweinfurt); H.L. Fehm (University Hospital, Lübeck); M. Morcos (University Hospital, Heidelberg); F. Beuschlein (University of Freiburg, Freiburg); M. Brauckhoff (University Hospital, Halle); N. Reisch (University Hospital, Munich); K. Muessig (University Hospital, Tübingen); C. Fottner (University Hospital, Mainz); K. Hengst (University Hospital, Münster); and J. Lübbren (Endokrinologikum, Hamburg).

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