Improved Survival in Patients with Stage II Adrenocortical Carcinoma Followed Up Prospectively by Specialized Centers

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Context: Median survival in stage II adrenocortical carcinoma (ACC) differs widely in published series ranging between 23 and more than 60 months. We hypothesized that these results may have been affected by a referral bias because many patients may contact specialized centers only after recurrence.

Objective: The objective of the study was a comparison of outcome in patients with stage II ACC who were followed up prospectively early after surgery and were counseled by a specialized center (prospective group) with patients who registered with the German ACC registry later than 4 months after diagnosis (retrospective group).

Patients/Methods: The study was a cohort analysis in 149 adult patients with stage II ACC.

Results: Patients who were followed up prospectively (n = 30) had a lower recurrence rate and a superior 5-yr survival compared with the 119 patients in the retrospective group (30 vs. 74%, P < 0.01 and 96 vs. 55%, P < 0.05, respectively). In the retrospective group, 67% of the patients had registered only after disease recurrence. In the remaining patients, the recurrence rate was low (21%), and the 5-yr survival was greater than 95%. More patients in the prospective group received adjuvant mitotane (53 vs. 16%, P < 0.001), and adjuvant mitotane was associated with improved survival [hazard risk 0.35 (95% confidence interval 0.13–0.97); P = 0.04]. However, the survival advantage was maintained when only patients without mitotane therapy were analyzed.

Conclusions: Patients who are followed up prospectively after surgery for stage II ACC and receive early specialized care have a much better prognosis than previously reported due to a major referral bias in previous series and use of adjuvant mitotane. These findings will impact on the perception of prognosis in newly diagnosed stage II ACC. (J Clin Endocrinol Metab 95: 4925–4932, 2010)

Adrenocortical carcinoma is known to be a highly aggressive malignancy, and hence, the prognosis of patients with adrenocortical carcinoma is dismal (1–3). Overall 5-yr survival was reported to be only 16–44% (4–12). Prognosis is stage dependent (13, 14): for patients presenting with localized disease, complete tumor resection is potentially curative. In contrast, in advanced disease, the adrenolytic agent mitotane and cytotoxic che-

Abbreviations: HR, Hazard risk; CI, confidence interval; Rx, uncertain resection status.
motherapies usually exhibit only limited and temporary efficacy and are associated with significant side effects (1, 15–19). In a historical series, most patients were diagnosed with advanced disease (stage IV) (20–23). Today, due to more widely available imaging, more patients present with earlier stages, which are amenable to complete resection (14, 24), although some investigations indicate that the proportion of patients with distant metastasis has remained stable since 1985 (25). However, even in patients with stage II adrenocortical carcinoma, undergoing surgery with curative intent relapse is common. Recurrence rates of up to 85% have been observed (6), and the 5-yr survival in stage II patients ranges from 38 to 61% in different series (8–10, 12, 14, 26). These figures are discouraging and certainly contribute substantially to the psychological burden of patients after surgery for adrenocortical carcinoma.

According to our experience at the University Hospital of Würzburg, where the German adrenocortical carcinoma registry is maintained, many patients initially diagnosed with early stage adrenocortical carcinoma are referred to specialized centers only after recurrence. Thus, we hypothesized that reports on recurrence rates and survival in patients with early-stage adrenocortical carcinoma, including from our own department, may have been seriously affected by patient selection. More specifically, patients who remain disease free after surgery for stage I-II adrenocortical carcinoma may never contact specialized centers and therefore may have been underrepresented in published series.

The German adrenocortical carcinoma registry was established in 2003 (27). In the beginning data collection was mainly retrospective and many patients had already experienced tumor relapse at the time point at which they were recorded. However, as this national registry became more widely known, an increasing number of patients have been registered close to initial diagnosis and first surgery. Confronted with a rare and highly malignant disease, attending doctors or their patients today seek early advice from a specialized center or contact the German adrenocortical carcinoma registry. These patients are then counseled during a personal visit or by phone and a structured approach to further care (28, 29) is provided. All patients are followed up regularly, even though they are not necessarily treated at a specialized center or even may receive no treatment at all.

Thus, based on the data from the German adrenocortical carcinoma registry, the objective of our study was to evaluate whether and to which extent survival rates in patients with adrenocortical carcinoma are influenced by patient selection and early specialized care. To this end we focused on stage II disease and analyzed whether patients who registered around the time of diagnosis and thus could be followed up prospectively and unselected in specialized centers show the same poor survival as do stage II patients from the adrenocortical carcinoma registry in general. We decided not to include stage I patients because in nonrelapsing patients with stage I adrenocortical carcinoma, there may remain doubts whether the tumor was actually an adrenocortical carcinoma.

### Patients and Methods

#### Patients

At the time of analysis (May 2009), the German adrenocortical carcinoma registry contained initial and follow-up data of 532 patients. Data on symptoms, diagnostic and surgical procedures, histopathological details, and treatment were collected by trained medical personnel using structured evaluation forms as described previously (14, 30). The follow-up data were obtained approximately every 3 months. The German adrenocortical carcinoma registry was approved by the Ethics Committee at the University of Würzburg, and the patients gave written informed consent. In all cases, the clinical diagnosis had been confirmed by histopathology. In 56% of the patients, paraffin-embedded adrenal tissue was provided to the reference pathologist of the registry (Wolfgang Saeger, Hamburg, Germany) to review the histopathological diagnosis.

Because not only the quality of imaging but also treatment and supportive care have changed over time, only patients in whom adrenocortical carcinoma was diagnosed in or after 1990 were included (n = 489). Patients with too short follow-up time (<12 months, n = 39) or too few data to accurately determine stage at presentation (n = 12) were excluded from the analysis. Because adrenocortical carcinoma in children may have a different pathogenesis and prognosis, children younger than 16 yr were also excluded (n = 36). In summary, this resulted in a set of 149 patients who were included in the data analysis.

Stage designation was based on the recently published European Network for the Study of Adrenal Tumours criteria, which have been found to be superior to the current World Health Organization staging system (14, 31): stage I, a tumor diameter of 5 cm or less (n = 19); stage II, a tumor diameter of more than 5 cm (n = 149); stage III, tumor infiltration of neighboring structures, venous tumor thrombus in vena cava or renal vein, or positive lymph nodes (n = 112); and stage IV, distant metastases (n = 122).

For further analysis, the 149 patients initially diagnosed with stage II disease were grouped according to the registration date. The designated prospective subgroup comprised patients who were enrolled in the German adrenocortical carcinoma registry shortly after having been diagnosed, i.e., within 4 months (120 d) after the resection of the primary tumor. This 4-month cutoff was predefined. It represents a compromise between avoiding a referral bias also in the prospective group and maintaining a sufficient sample size. The second subgroup, which we called retrospective, comprised all patients who registered later than 4 months after primary surgery.

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Statistics

Continuous nonparametric variables were presented as the median values and range. Patient’s characteristics between both subgroups were compared by Mann-Whitney U test and χ² test. Disease-specific survival was defined as the time elapsed from primary diagnosis to death due to adrenocortical carcinoma. Patients who were alive or who had died of other causes were censored. Survival analysis was calculated using the Kaplan-Meier method, and the differences between groups were assessed with log-rank statistics. Disease-free survival was analyzed only in patients after radical resection and was defined as time from the date of tumor resection to the first evidence of relapse or last follow-up without evidence for disease. The Cox proportional hazards model was used for multivariate analysis to adjust for sex, age, resection status, adjuvant mitotane, and mitotic index. Descriptive P values were provided for the assessment of differences between indicated groups of patients. Data were analyzed using the Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL).

Results

Patients’ characteristics

The characteristics of the different study populations, all patients, and the respective subgroups, are listed in Table 1.

Of the 149 patients with stage II disease, 30 patients qualified for the prospective follow-up group, whereas the retrospective group consisted of the remaining 119 patients who had registered later than 4 months after resection of the

<table>
<thead>
<tr>
<th>TABLE 1. Patient’s characteristics</th>
<th>All stage II patients</th>
<th>Prospective group</th>
<th>Retrospective group</th>
<th>P value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 149</td>
<td>30</td>
<td>119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female 97 (65%)</td>
<td>24 (80%)</td>
<td>73 (61%)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Male 52 (35%)</td>
<td>6 (20%)</td>
<td>46 (39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median 48</td>
<td>46</td>
<td>49</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Range 17–87</td>
<td>19–77</td>
<td>17–87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to ≤10 75 (50%)</td>
<td>14 (47%)</td>
<td>61 (51%)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>&gt;10 74 (50%)</td>
<td>16 (53%)</td>
<td>58 (49%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0 102 (68%)</td>
<td>25 (84%)</td>
<td>77 (65%)</td>
<td>0.12 b</td>
<td></td>
</tr>
<tr>
<td>R1 9 (6%)</td>
<td>1 (3%)</td>
<td>8 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R2 1 (1%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx 33 (22%)</td>
<td>3 (10%)</td>
<td>30 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data 4 (3%)</td>
<td>3 (3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotane 35 (23%)</td>
<td>16 (53%)</td>
<td>19 (16%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Tumorbed irradiation 13 (9%)</td>
<td>2 (7%)</td>
<td>11 (9%)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Reference histology available 84 (56%)</td>
<td>28 (93%)</td>
<td>56 (47%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Weiss score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median 5</td>
<td>5</td>
<td>5</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Range 2–9</td>
<td>2–8</td>
<td>3–9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data 60 (40%)</td>
<td>2 (7%)</td>
<td>58 (49%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotic activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5/50 HPF c 24 (23%)</td>
<td>9 (32%)</td>
<td>15 (20%)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>≥5/50 to &lt;10/50 HPF c 18 (17%)</td>
<td>3 (7%)</td>
<td>15 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10/50 HPF c 61 (59%)</td>
<td>16 (57%)</td>
<td>45 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data 46 (31%)</td>
<td>2 (7%)</td>
<td>44 (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up time in patients still alive (median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 37.7</td>
<td>25.2</td>
<td>50.4</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Disease recurrence 97 (65%)</td>
<td>9 (30%)</td>
<td>88 (74%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>At the time of registration 80 (54%)</td>
<td>0 (0%)</td>
<td>80 (67%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Treatment for recurrent disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection 56 (57%)</td>
<td>3 (33%)</td>
<td>53 (60%)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy 7 (7%)</td>
<td>0 (0%)</td>
<td>7 (8%)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Mitotane and/or cytotoxic drugs 58 (60%)</td>
<td>6 (66%)</td>
<td>52 (59%)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Death 54 (36%)</td>
<td>1 (3%)</td>
<td>53 (42%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

HPF, High-power field.

a Difference between prospective and retrospective groups.

b R0 vs. the other groups (R1, R2, Rx) together.

c Calculation of percentage based only on patients with available data.

d Including four patients who died of causes not related to adrenocortical carcinoma.
primary tumor [median time of registration after surgery 27 months (4.1–153 months) vs. 64 d (0–104 d); $P < 0.001$].

There were no statistically significant differences between both subgroups concerning sex, age, tumor size, and frequency of adjuvant tumor bed irradiation. Similarly, neither mitotic count nor Weiss score differed between the two groups. However, histopathological details were missing in a significant number of cases in the retrospective subgroup. The retrospective group included more patients with uncertain resection status (Rx) (25% vs. 10%, $P = 0.03$).

A major difference was seen in the use of adjuvant mitotane: only 16% of the patients in the retrospective group received mitotane compared with 53% of the patients with prospective follow-up ($P < 0.001$).

**Recurrence rates and treatment for recurrence**

All patients of the prospective subgroup were macroscopically disease free when they were enrolled in the German adrenocortical carcinoma registry. Among them, nine patients developed tumor relapse during follow-up, corresponding to a recurrence rate of 30%. In contrast, the recurrence rate in the retrospective subgroup amounted to 74% ($P < 0.001$). Importantly, most patients in this group (67%) had already experienced tumor recurrence at the time of registration. In contrast, of those 39 patients in the retrospective group who registered without evidence of tumor relapse [median time of registration after surgery was 16 months (4–101 months)], only eight (21%) experienced tumor relapse during follow-up.

Surgery for recurrent disease was performed in 53 of 88 patients in the retrospective group compared with three of nine patients in the prospective group ($P = 0.12$).

**Impact of the registration time on survival rates**

The 5-yr survival of all patients with stage II disease was 58%. However, when the prospective and retrospective subgroups were analyzed separately, 5-yr survival differed dramatically (Fig. 1): patients who registered shortly after diagnosis had a significantly better 5-yr survival compared with patients who enrolled later in the course of the disease (96% vs. 55%, $P = 0.02$). Improved survival was maintained when the analysis included only patients without adjuvant mitotane treatment (Fig. 2, 5-yr survival 92% vs. 52%; $P = 0.15$), although the difference was no longer significant, most likely due to the small number of prospectively followed patients who did not receive adjuvant mitotane. After adjustment for sex, tumor size, resection status, and mitotic count, the disease-specific survival was statistically not significantly different between both groups, but patients with prospective follow-up had a dramatic lower risk of death compared with the patients of the retrospective subgroup [hazard risk (HR) 0.19, 95% confidence interval (CI) 0.03–1.39; $P = 0.10$].

Including adjuvant mitotane as an additional covariable in the multivariate analysis did not alter the results significantly (HR 0.21, 95% CI 0.03–1.55; $P = 0.21$).

To evaluate the influence of the arbitrarily chosen cut-off time on the two groups, we performed an additional analysis choosing a cutoff of 6 months after diagnosis instead of 4 months for enrolling in the registry for the definition of the prospective group. This increases the prospective group to 39 patients and the difference between the groups becomes significant also in multivariate analyses with a HR of 0.13 95% CI 0.02–0.93; $P = 0.04$.

Patients from the retrospective group who were free of recurrence at the time of inclusion in the registry ($n = 39$) had a high 5-yr survival of greater than 95% (Fig. 3).
Impact of mitotane on survival

Patients who received adjuvant mitotane displayed a significantly better 5-yr survival than did the patients without mitotane treatment [Fig 4, 87 vs. 53%, HR for death 0.35 (95% CI 0.13–0.97); \( P = 0.04 \)]. In multivariate analysis, after adjustment for resection status and mitotic count, adjuvant mitotane treatment was still associated with a risk reduction of 62% (HR 0.38, 95% CI 0.12–1.28; \( P = 0.11 \)). A similar trend was seen for the association of adjuvant mitotane and disease-free survival in patients with complete resection (HR for recurrence: 0.58; 95% CI 0.29–1.15; \( P = 0.12 \)).

Discussion

Our study demonstrates for the first time that survival in unselected patients with localized adrenocortical carcinoma who are followed up prospectively after surgery and receive early specialized care is far superior to survival data in previously published reports. The key factor responsible for this extraordinary difference is most likely a major referral bias in previous patient series. Early counseling by a specialized center leading to an increased use of adjuvant mitotane may also have contributed to the observed difference.

The overall 5-yr survival of our study patients presenting with stage II disease was 58%. This is very much in line with existing data. Previously published survival curves of patients with stage II disease reported in these series are given in Fig. 5. In 1997 Bellantone et al. (8) reported 188 cases of adrenocortical carcinoma collected in the Italian national registry for adrenocortical carcinoma. They noticed a 5-yr survival of about 52% in patients with stage I or II disease. Schulick and Brennan (9) studied the outcome of 113 patients who presented to Memorial Sloan-Kettering Cancer Center (New York, NY) for treatment of adrenocortical carcinoma. They noticed a 5-yr survival of about 52% in patients with stage I or II disease. Schulick and Brennan (9) studied the outcome of 113 patients who presented to Memorial Sloan-Kettering Cancer Center (New York, NY) for treatment of adrenocortical carcinoma. They noticed a 5-yr survival of about 52% in patients with stage I or II disease. Schulick and Brennan (9) studied the outcome of 113 patients who presented to Memorial Sloan-Kettering Cancer Center (New York, NY) for treatment of adrenocortical carcinoma. They noticed a 5-yr survival of about 52% in patients with stage I or II disease.
patients had their primary operation at the M. D. Anderson Cancer Center. No details were provided on how many of the patients were sent to the cancer center only after disease recurrence. However, it was stated that this was the majority of patients and that the recurrence rate observed in this series may thus overestimate the true risk of recurrence (26). The same group very recently updated their series and demonstrated that the 28 patients in whom primary surgery was performed at M. D. Anderson and who were followed up prospectively had a clearly better survival than the group with surgery at other institutions (32). These observations are in close agreement with our findings. Unfortunately, however, the problem of a referral bias has not yet been addressed in other patient cohorts.

In contrast to the overall cohort, the small subgroup of patients who registered shortly after resection of the primary tumor and who could thus be followed up in a prospective manner had an impressively better survival than the patients of the retrospective group. According to our results, the 5-yr survival of patients presenting with stage II disease can be estimated at approximately 95%, with a recurrence rate of 30%. As suspected, the majority of patients who enrolled later in the course of the disease had already developed local recurrence or distant metastasis at the time of registration. Because these patients clearly predominate, the survival curve is shifted to poorer outcome, indicating a selection bias. This is supported by the much superior survival of those patients from the retrospective group who were included in the registry without evidence of recurrence at a median time of 16 months after diagnosis. These patients had an excellent 5-yr survival of greater than 95%, further supporting the concept of an important referral bias in previously published series.

Because the two subgroups differed mainly in the frequency of adjuvant mitotane treatment, we paid particular attention to the impact of mitotane. Since its introduction in 1960, mitotane plays a pivotal role in treatment of adrenocortical carcinoma, especially in advanced disease. Its benefit in an adjuvant setting still is a matter of debate (19, 33–38). In contrast to previous studies with small cohorts (for review see Ref. 16), a large retrospective multicenter study recently found that adjuvant mitotane treatment can reduce the risk of recurrence and death in patients with adrenocortical carcinoma (30). Based on these and more recent observations (39), adjuvant treatment with mitotane is more frequently used in recent years. Thus, it is not surprising that more patients in the prospective subgroup were treated with mitotane because this group contained only patients diagnosed with adrenocortical carcinoma after the initiation of the German adrenocortical carcinoma registry in 2003. However, when analyzing only patients without mitotane therapy, a difference in survival between the two subgroups persisted, again pointing to the importance of the inclusion time.

Although our study did not specifically aim to address the issue of adjuvant mitotane therapy, our findings support the use of mitotane after radical surgery. In the patients analyzed in this study, the use of adjuvant mitotane was associated with an increased 5-yr survival. In addition, disease-free survival tended to be much better (42% risk reduction for recurrence), although statistical significance was not reached, probably due to the small sample size.

It can be assumed that patients who are referred to specialized centers early after diagnosis benefit from not only the more frequent use of adjuvant treatment in these centers but also regular and close-meshed follow-up, allowing early reoperation in case of recurrence. However, a lower percentage of patients in the prospective group suffering from recurrence had surgery for tumor relapse. A number of studies have suggested a beneficial effect of surgery for recurrent disease (6, 8, 9, 40). However, due to methodological problems (e.g. retrospective analysis, comparability of patients), it has been difficult to prove the benefit of such surgery for survival beyond doubt. Furthermore, we did not find evidence for differences in drug treatment for recurrent disease between the two groups (Table 1).

Long-term survivors are often thought to have had actually an adrenal adenoma, not a carcinoma, because histological differentiation between both tumor entities may be difficult. To minimize the chance to include benign adrenal adenoma or nonadrenocortical malignancies, the paraffin-embedded tumor tissue of our study patients was reevaluated by the reference pathologist of the German adrenocortical carcinoma registry in many cases. In particular, the histopathological diagnosis was reviewed in all but two patients of the prospective subgroup. In one of these two cases, however, the local pathologist had found a Ki-67 of 40%, and the patient developed tumor relapse, findings that are not compatible with a benign adenoma.

Our study has important limitations. Because even today most patients diagnosed with stage II adrenocortical carcinoma contact the German adrenocortical carcinoma registry only after tumor relapse, the statistical power of our study is clearly limited by the small number of patients with prospective follow-up and the relatively short follow-up period for the prospective group. However, because the observed difference between the two groups is large and will certainly impact the risk perception in stage II adrenocortical carcinoma, our findings may stimulate reanalysis of previous series and thereby may help to quickly generate additional information in this important area.

In conclusion, our findings indicate that survival of patients presenting with stage II disease shortly after surgery and receiving early specialized care is substantially better.
than currently supposed. A referral bias in previously published series (including from our own center) has led to overrepresentation of patients with recurrent disease and poor outcome, whereas patients cured by surgery alone may have been grossly underrepresented. In addition, more frequent use of adjuvant mitotane may have contributed to the observed improved survival. These findings are likely to impact the well-being of patients with stage II adrenocortical carcinoma and on counseling by their respective physicians.

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