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ORIGINAL ARTICLE – ENDOCRINE TUMORS

# Recurrence of Adrenal Cortical Carcinoma Following Resection: Surgery Alone Can Achieve Results Equal to Surgery Plus Mitotane

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## ABSTRACT

**Background.** A recent nonrandomized interinstitutional study reported that adjuvant mitotane following surgery for adrenocortical carcinoma (ACC) was associated with decreased recurrence. Because of the limitations of this study, we investigated the influences of surgery and adjuvant mitotane in a large series of ACC patients evaluated and treated at a single referral center.

**Study Design.** Retrospective evaluation of patients followed at a single institution after surgery for ACC.

**Results.** 218 patients with ACC underwent primary resection either at the index institution [surgery index (SI), $n = 28$] or an outside institution [surgery outside (SO), $n = 190$] and had a median follow-up of 88 months. SI patients had a superior disease-free survival compared with SO patients (median 25 versus 12 months, $P = 0.003$), and SI patients also had a superior overall survival compared with SO patients (median not reached versus 44 months, $P = 0.02$). Factors predicting increased risk of recurrence on multivariate analysis were surgery at an outside institution [hazard ratio (HR) 2.56, 95% confidence interval (CI) 1.44–4.53, $P = 0.001$] and no treatment with adjuvant mitotane (HR 1.95, 95% CI 1.06–3.59, $P = 0.03$), and those predicting a poorer survival were advanced stage at presentation ($P = 0.01$) and surgery at an outside institution (HR 2.62, 95% CI 1.31–5.25, $P = 0.007$).

**Conclusions.** The recurrence rate of the index group (50%) in the current series, the overwhelming majority of whom did not receive adjuvant mitotane, is indistinguishable from that reported for those who received adjuvant mitotane (49%) in the recent interinstitutional report, emphasizing the importance of completeness of initial surgery in the management of patients with ACC.

Adrenal cortical carcinoma (ACC) is a rare endocrine neoplasm with poor prognosis. Most patients with ACC are diagnosed at an advanced stage of disease. Early diagnosis is uncommon; when diagnosed, ACCs are usually large and have invaded adjacent organs, even if metastatic spread to distant sites is not present.[1,2] Although complete surgical resection remains the only potentially curative treatment for patients who present with localized disease, recurrence following surgery is common. The role of mitotane, alone or in combination, as adjuvant therapy following resection for ACC remains controversial; data from randomized studies is lacking. Some investigators have found no benefit from adjuvant mitotane.[3–6] However, a recent nonrandomized interinstitutional study reported that the addition of adjuvant mitotane to surgery for ACC was associated with a decreased recurrence rate [49% with mitotane versus 73% (Italian group) and 91% (German group) without mitotane].[7] Based on this report, there has been increased interest in the use of mitotane as adjuvant therapy for patients with ACC. However, the investigators' analysis must be interpreted with caution.[8,9] First, the very high recurrence rate in the control groups suggests that at least some patients in these groups had incomplete surgery.[10,11] Second, an imbalance in standardized restaging among the reporting institutions over the 20 years of the



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study could have resulted in ascertainment or lead-time bias with regard to recurrences. Third, there is no information provided regarding crossover treatment with mitotane among control patients who recurred. Finally, the authors could not consistently demonstrate an overall survival benefit associated with adjuvant mitotane therapy. Because of limitations such as these, resulting in part from the multi-institutional nature of the study, we investigated the relationships between surgery, adjuvant mitotane therapy, and outcome in a large series of ACC patients evaluated and treated at a single tertiary care referral center.

## PATIENTS AND METHODS

### *Patients*

Approval from The University of Texas M.D. Anderson Cancer Center's (MDACC) institutional review board was obtained for this study. The records of all patients evaluated at our institution between January 1991 and June 2008 for histologically confirmed ACC were retrospectively reviewed from a prospectively maintained database. We evaluated the subset of patients who underwent primary resection for their disease. Patients who did not undergo surgical resection due to extent of disease were excluded. Patients were divided into two groups for analysis of outcome based on where their primary surgery was performed: (1) those who underwent primary resection at MDACC by one of three experienced endocrine surgeons (N.D.P., D.B.E., J.E.L.) (index institution), and (2) those who underwent resection prior to referral and were subsequently referred to MDACC (outside institution). A second analysis was subsequently performed in which the patients were divided into two groups based on treatment with adjuvant mitotane: (1) those who received adjuvant mitotane, and (2) those who did not receive adjuvant mitotane.

Data on patient demographics, stage at presentation, tumor size, functional status, type of surgical procedure, extent of surgery, completeness of surgery, and histopathologic resection margins were evaluated. Stage at presentation was based on the Lee classification system: stage I and II patients have noninvasive tumors $\leq$5 cm and >5 cm, respectively; stage III patients have locoregional extension of their tumors and/or regional adenopathy; and stage IV patients have distant metastases.[1] Extent of surgery was designated as *adrenal resection alone* versus *adrenal resection in combination with one or more adjacent organs and/or inferior vena cava*. Completeness of surgery was designated as grossly *complete* (R0), *incomplete* (R1) or *undetermined* by evaluation of the operative note. Histopathologic resection margin was determined to be *negative* (microscopic R0), *positive* (microscopic R1) or *undetermined* by evaluation of the pathology report. Overall survival (OS) duration for the study population was calculated from date of diagnosis to date of death, or to date of last follow-up evaluation for patients still alive at conclusion of follow-up. Disease-free survival (DFS) duration was calculated from date of diagnosis to date of tumor recurrence, or to date of last follow-up evaluation for patients without recurrence at conclusion of follow-up. Disease recurrence was determined based on a combination of clinical and radiographic evidence; biopsy confirmation of recurrence was not required. Adjuvant therapy with mitotane was considered to have been administered when mitotane was started within 6 months of surgery and continued for at least 2 months. As detailed in the "Results" section, we also investigated a more restrictive definition for adjuvant mitotane, in which inclusion was limited to those patients who received mitotane within 2 months of surgery and continued for at least 2 months.

### *Statistical Analysis*

The Kaplan-Meier method was used to determine OS and DFS. Log-rank analysis was used to evaluate differences in OS and DFS between subgroups. $P \leq 0.05$ was considered statistically significant. Location of initial surgery (index versus outside), adjuvant mitotane (yes versus no), and additional potential prognostic factors (gender, age, stage at presentation, and tumor functional status) were included in a multivariate model using Cox proportional hazard regression. Categorical data was analyzed by chi-square test or Fisher's exact test as indicated. Continuous data was analyzed by Student's *t*-test. All analyses were performed using SAS 9.1 (SAS Institute Inc, Cary, NC).

## RESULTS

Of 233 consecutive patients evaluated for ACC, 15 were excluded because they did not undergo surgical resection of their primary tumor owing to extensive metastatic disease at presentation ($n = 14$) or a locally advanced, unresectable primary tumor ($n = 1$), leaving 218 patients for analysis. Of these 218 patients, 28 had their primary operation at the index institution (MDACC) and the remaining 190 were referred to our institution after their initial surgery.

Demographic data for the index and outside patient groups is summarized in Table 1. Index patients were on average slightly older than outside patients (median age at diagnosis 51 versus 45 years, Student's *t*-test, $P = 0.04$). Otherwise, the index and outside patient groups were well

**TABLE 1** Demographics, stage, and surgical details of 218 patients who underwent primary resection of adrenal cortical carcinoma at either the index institution (MDACC) or an outside institution

| | Index institution ($n = 28$) | Outside institution ($n = 190$) | Odds ratio (index versus outside) | 95% CI | $P$ value |
|---|---|---|---|---|---|
| Age, median (range), years | 51 (20–79) | 45 (3–78) | – | – | 0.04 |
| Gender (F:M) | 1.5:1 | 2:1 | 0.79 | 0.35–1.78 | 0.67 |
| Size, median (range), cm | 12.0 (4–30) | 12.0 (3–24)[a] | – | – | 0.13 |
| Functioning (%) | 67.9 | 53.2 | 1.86 | 0.80–4.34 | 0.16 |
| Lee stage (%) | | | | | |
| I-II | 9 (32) | 73 (45)[a] | – | – | – |
| III | 16 (57) | 84 (52)[a] | – | – | – |
| IV | 3 (11) | 6 (4)[a] | – | – | 0.17 |
| Incomplete resections (total) | 0 (28) | 12 (126)[a] | – | – | 0.13 |
| Multiorgan resection (total) | 15 (28) | 67 (182)[a] | 1.98 | 0.88–4.41 | 0.10 |
| Histologically involved margins (total) | 3 (27)[a] | 31 (99)[a] | 0.27 | 0.08–0.98 | 0.05 |

[a] Uncertain status in 1 or more patients

balanced with regards to gender distribution, primary tumor size, presence of clinical evidence for hormone overproduction (functional status), and stage at presentation.

All index patients underwent open resection of their primary tumors. In contrast, 18 (9%) of outside patients underwent laparoscopic resection of their primary tumors. All index patients had grossly complete tumor resections. In contrast, resections were incomplete in 12 of 126 (10%) outside patients for whom resection status could be assessed ($P = 0.13$). Multiorgan resection (adrenal plus at least one additional adjacent organ) was performed in 54% of index patients and 37% of outside patients. Histologically involved margins were documented in 3 of 27 (11%) index patients compared with 31 of 99 (31%) outside patients ($P = 0.05$); margin status could not be assessed in 1 index patient and 91 outside patients.

### *Outcome of Surgically Treated Patients*

The median follow-up of the 218 patients was 88 months, and follow-up was complete through February 2009. At the conclusion of follow-up, 172 of 211 (82%) patients had recurred, including 14 of 28 (50%) index patients and 158 of 183 (86%) outside patients. At conclusion of follow-up, 138 (63%) patients had died, including 9 of 28 (32%) index patients and 129 of 190 (68%) outside patients. The median DFS of the entire group was 13 months, and the median OS was 47 months. Index patients had a superior DFS compared with outside patients (median 25 versus 12 months, $P = 0.003$) (Fig. 1), and index patients also had a superior OS compared with outside patients (median not reached versus 44 months, $P = 0.02$) (Fig. 2).

### *Outcome of Patients Treated with Adjuvant Mitotane*

Twenty-two of 218 patients (10%) received at least 2 months of adjuvant mitotane within 6 months of surgery (Table 2). Sixteen patients started adjuvant mitotane within 2 months following initial surgery, 4 patients more than 2 months but less than 4 months following surgery, and the remaining 2 patients more than 4 months but less than 6 months following surgery; 3 patients who received adjuvant mitotane more than 6 months following surgery were excluded from analysis of the effect of adjuvant mitotane on outcome. Patients who received or did not receive adjuvant mitotane were relatively well balanced with regard to basic demographics; we could not detect a selection bias with regard to age, gender, tumor functional status or stage at presentation. There were nonsignificant trends associating laparoscopic resection ($P = 0.07$), advanced stage of disease ($P = 0.12$), and involved margin status ($P = 0.13$) with adjuvant mitotane therapy. Twelve of 22 (55%) patients who received adjuvant mitotane recurred, compared with 160 of 190 (84%) who did not receive adjuvant mitotane. Eight of 22 (36%) patients who received adjuvant mitotane died, compared with 130 of 196 (66%) who did not receive adjuvant mitotane. The median DFS of those who received adjuvant mitotane was 30 months, compared with 12 months for those who had not received mitotane ($P = 0.05$) (Fig. 3). The median OS for those who received adjuvant mitotane was 64 months, compared with 43 months for those who did not receive mitotane ($P = 0.32$) (Fig. 4). Two of the three index patients treated with adjuvant mitotane have not recurred after follow-up intervals of 8, 14, and 81 months, and all three were alive at the conclusion of follow-up. In contrast,

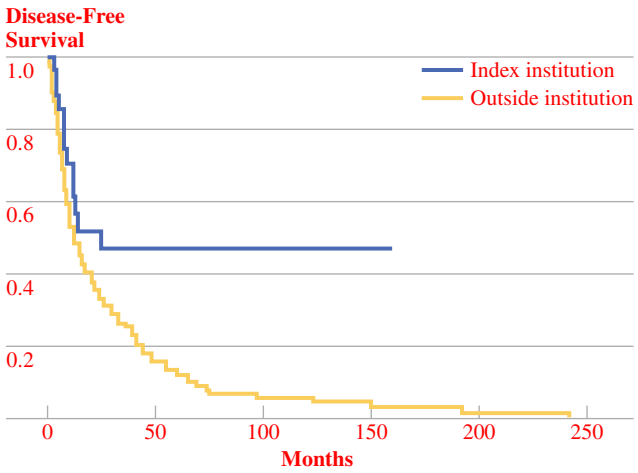


**FIG. 1** Disease-free survival (DFS) of patients who underwent primary surgery at the index institution (MDACC) versus an outside institution. Median follow-up 88 months; median DFS index versus outside, 25 versus 12 months, $P = 0.003$, HR 2.22 (1.28–3.85)

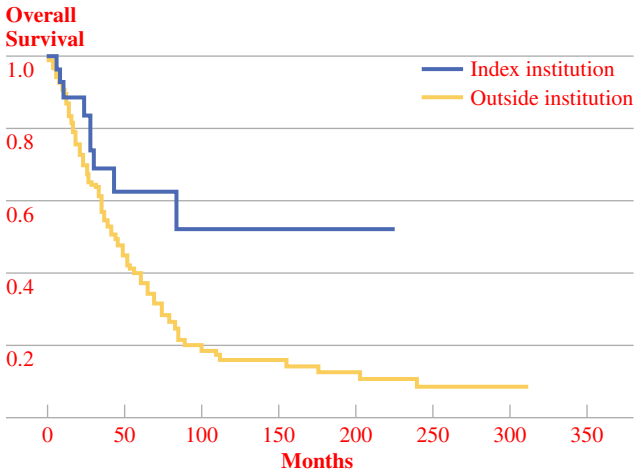


**FIG. 2** Overall survival (OS) of patients who underwent primary surgery at the index institution (MDACC) versus an outside institution. Median follow-up 88 months; median OS index versus outside, not reached versus 44 months, $P = 0.02$, HR 2.13 (1.08–4.18)

10 of 18 (56%) outside patients treated with adjuvant mitotane have recurred, with a median DFS of 30 months, and 8 outside adjuvant mitotane patients have died (44%), with a median OS of 64 months. When the three index patients who received adjuvant mitotane were removed and the analysis limited to the outside group, treatment with adjuvant mitotane was no longer significantly associated with improved DFS (30 versus 12 months, $P = 0.11$), and the relationship of adjuvant mitotane therapy to OS remained nonsignificant (64 versus 44 months, $P = 0.73$).

Because of the potential role of adjuvant mitotane in improving DFS following primary surgery for ACC, we investigated the outcome of patients treated according to the alternative strategy of withholding mitotane until disease recurrence. One hundred eight of 196 patients (55%) who did not receive adjuvant mitotane following their initial resection received mitotane following recurrence (crossover treatment), either as adjuvant therapy following resection of local-regional or metastatic ACC ($n = 5$), or as treatment for measurable recurrent disease ($n = 103$). We compared the outcome of patients treated with adjuvant mitotane following their initial operation ($n = 22$) with those treated according to the alternative "intention-to-treat" strategy of mitotane only if recurrence developed. This latter group included the 108 patients who received mitotane following a recurrence, as well as 24 patients who did not receive mitotane as initial adjuvant therapy and also never recurred, since such patients reflected the intended treatment strategy of withholding mitotane unless a recurrence developed (total $n = 132$). Patients treated according to the alternative strategy of mitotane only following recurrence had a median DFS of 14 months, compared with 30 months for patients treated with mitotane as primary adjuvant therapy following initial surgery [odds ratio (OR) 1.54, 95% CI 0.85–2.81, $P = 0.16$].

### *Univariate and Multivariate Predictors of Outcome in Surgically Treated ACC Patients*

Potential and actual predictors of DFS and OS in patients who underwent surgery for ACC are summarized in Tables 3 and 4, respectively. Variables investigated in univariate analysis included gender, age, primary tumor size, stage at presentation, tumor functional status, location of surgery (index versus outside), and adjuvant mitotane treatment. These same variables were included in the multivariate model with the exception of tumor size, since size is included in the staging variable. Margin status was excluded from analysis due to the high proportion (42%) of patients with missing margin status. The factors significantly associated with increased risk of disease recurrence following surgery on univariate analysis were surgery at an outside institution and no treatment with adjuvant mitotane. The factors significantly associated with poorer survival following surgery on univariate analysis were a hormonally active tumor and surgery at an outside institution. The factors independently predicting increased risk of disease recurrence following surgery on multivariate analysis were surgery at an outside institution (HR 2.56 95% CI 1.44–4.53, $P = 0.001$) and no treatment with adjuvant mitotane (HR 1.95, 95% CI 1.06–3.59, $P = 0.03$). The factors independently predicting poorer survival following surgery on multivariate analysis were advanced

**TABLE 2** Demographics, stage, and surgical details of patients who either did or did not receive adjuvant mitotane following surgery for adrenal cortical carcinoma

| | Patients who received adjuvant mitotane ($n = 22$) | Patients who did not receive adjuvant mitotane ($n = 196$) | Odds ratio (adjuvant mitotane versus no adjuvant mitotane) | 95% CI | *P* value |
|---|---|---|---|---|---|
| Age, median (range), years | 50 (21–72) | 46 (3–79) | – | – | 0.64 |
| Gender (F:M) | 1.8:1 | 1.9:1 | 1.10 | 0.44–2.75 | 0.81 |
| Size, median (range), cm | 11.0 (5.2–21.0) | 12.0 (3.0–30.0) | – | – | 0.98 |
| Functioning (%) | 63.2 | 54.4 | 0.70 | 0.26–1.85 | 0.63 |
| Lee stage (%) | | | | | |
| I-II | 5 (26)[a] | 77 (45)[a] | – | – | – |
| III | 14 (74) | 86 (50) | – | – | – |
| IV | 0 | 9 (5) | – | – | 0.12 |
| Incomplete resections (total) | 0 (18)[a] | 12 (136)[a] | – | – | 0.36 |
| Multiorgan resection (total) | 10 (22) | 72 (189)[a] | – | – | 0.76 |
| Histologically involved margins (total) | 7 (16)[a] | 27 (110)[a] | 2.39 | 0.81–7.03 | 0.13 |

[a] Uncertain status in one or more patients

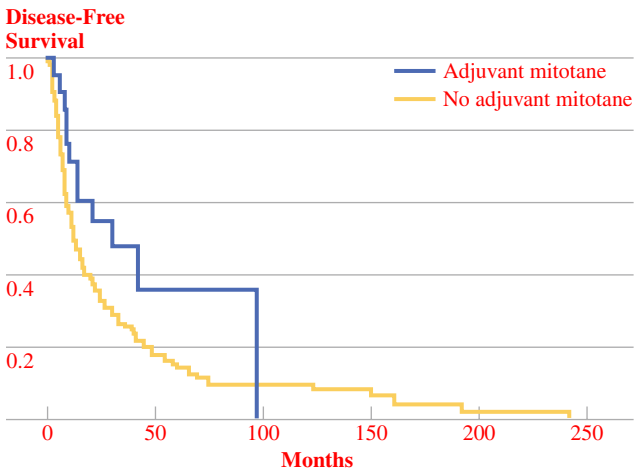


**FIG. 3** Disease-free survival (DFS) of patients who received adjuvant mitotane after their primary surgery versus those who did not receive adjuvant mitotane. Median follow-up 88 months; median DFS mitotane versus no mitotane, 30 versus 12 months, $P = 0.05$, HR 1.76 (0.98–3.16)

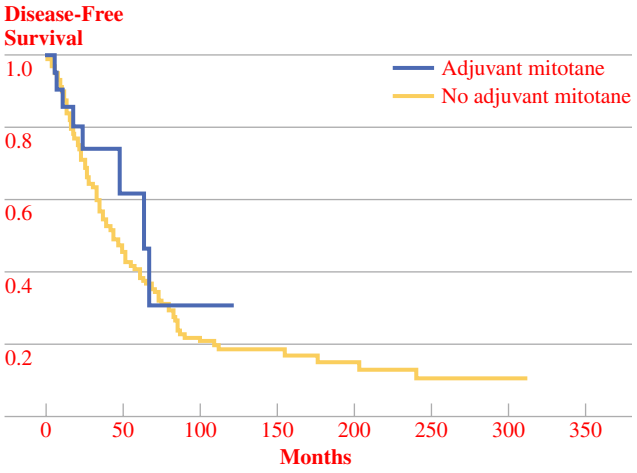


**FIG. 4** Overall survival (OS) of patients who received adjuvant mitotane after their primary surgery versus those who did not receive adjuvant mitotane. Median follow-up 88 months; median OS mitotane versus no mitotane, 64 versus 43 months, $P = 0.32$, HR 1.41 (0.69–2.88)

stage at presentation ($P = 0.01$) and surgery at an outside institution (HR 2.62, 95% CI 1.31–5.25, $P = 0.007$).

We performed sensitivity analysis to determine whether our data was sensitive to restricting the definition of adjuvant mitotane from starting treatment within 6 months of surgery to starting treatment within 2 months of surgery. When 2 months was used as the cutoff for initiation of adjuvant mitotane therapy, 6 of 22 patients were removed from the adjuvant group. Using this more restrictive definition, adjuvant mitotane therapy was no longer significantly associated with DFS (HR for no adjuvant mitotane 1.83, 95% CI 0.91–3.70, $P = 0.092$), and it remained a nonsignificant prognostic factor for OS.

## DISCUSSION

This study represents the largest reported series describing the outcome of patients with ACC treated with surgery and evaluated at a single institution.[3,12–15] The patients included in this study were seen at a large cancer center, yet most patients had their initial operation at a

**TABLE 3** Univariate and multivariate analysis of disease-free survival of patients who underwent primary resection for adrenal cortical carcinoma

| Variable | Univariate analysis | | | Multivariate analysis[a] | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *P* value | Hazard ratio | 95% CI | *P* value |
| Gender | | | | | | |
| Female versus male | 1.13 | 0.82–1.57 | 0.47 | 1.08 | 0.77–1.51 | 0.60 |
| Age | | | | | | |
| >45 years versus ≤45 years | 1.02 | 0.75–1.38 | 0.95 | 1.16 | 0.84–1.58 | 0.37 |
| Size | | | | | | |
| >5 cm versus ≤5 cm | 1.17 | 0.59–2.30 | 0.89 | NA | NA | NA |
| Lee stage | | | 0.92 | | | .46 |
| III versus I-II | 1.14 | 0.82–1.58 | | 1.19 | 0.85–1.68 | |
| IV versus I-II | 1.15 | 0.42–3.18 | | 1.84 | 0.65–5.22 | |
| Unknown versus I-II | 1.05 | 0.66–1.67 | | 0.96 | 0.60–1.55 | |
| Functioning | | | | | | |
| Yes versus no | 1.30 | 0.95–1.78 | 0.08 | 1.38 | 0.99–1.93 | 0.06 |
| Institution | | | | | | |
| Outside versus MDACC | 2.23 | 1.29–3.87 | 0.005 | 2.55 | 1.44–4.53 | 0.002 |
| Adjuvant mitotane (<6 months)[b] | | | | | | |
| No versus yes | 1.77 | 0.98–3.19 | 0.06 | 1.96 | 1.07–3.61 | 0.03 |

*NA* not analyzed

[a] The model for the multivariate analysis included gender, age, Lee stage, functional status, institution, and administration of mitotane (excluding three patients who received mitotane after 6 months)

[b] Excludes three patients who received mitotane after 6 months

**TABLE 4** Univariate and multivariate analysis of overall survival of patients who underwent primary resection for adrenal cortical carcinoma

| Variable | Univariate analysis | | | Multivariate analysis[a] | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *P* value | Hazard ratio | 95% CI | *P* value |
| Gender | | | | | | |
| Female versus male | 0.98 | 0.69–1.40 | 0.91 | 0.93 | 0.64–1.34 | 0.76 |
| Age | | | | | | |
| >45 years versus ≤45 years | 1.15 | 0.82–1.61 | 0.42 | 1.25 | 0.89–1.77 | 0.25 |
| Size | | | | | | |
| >5 cm versus ≤5 cm | 1.23 | 0.51–3.06 | 0.86 | NA | NA | NA |
| Lee stage | | | | | | 0.01 |
| III versus I-II | 1.34 | 0.91–1.95 | | 1.33 | 0.90–1.96 | |
| IV versus I-II | 2.93 | 1.23–6.95 | | 3.95 | 1.63–9.58 | |
| Unknown versus I-II | 1.09 | 0.65–1.84 | 0.08 | 0.99 | 0.58–1.68 | |
| Functioning | | | | | | |
| Yes versus no | 1.46 | 1.03–2.08 | 0.03 | 1.56 | 1.09–2.25 | 0.06 |
| Institution | | | | | | |
| Outside versus MDACC | 2.13 | 1.08–4.18 | 0.02 | 2.66 | 1.33–5.32 | 0.007 |
| Adjuvant mitotane (<6 months)[b] | | | | | | |
| No versus yes | 1.43 | 0.70–2.92 | 0.34 | 1.58 | 0.75–3.31 | 0.25 |

*NA* not analyzed

[a] The model for the multivariate analysis included gender, age, Lee stage, functional status, institution, and administration of mitotane (excluding three patients who received mitotane after 6 months)

[b] Excludes three patients who received mitotane after 6 months

nonreferral institution, and were only sent to a specialty center after adrenalectomy or disease recurrence. The fact that over 80% of the patients in this series developed recurrent ACC highlights the challenges in effective management of this disease.

While patients who underwent primary surgery at the index institution were slightly older than those who received surgery outside of the index institution, they were otherwise similar in their clinical presentation. Surgical management of index and outside patients was not identical, however. Laparoscopic resections were performed in 18 outside patients; this was never done for patients who had primary surgery at the index institution. Our prior reports document an unusually high rate of carcinomatosis in patients who have undergone laparoscopic resection of ACC, suggesting that laparoscopic resection of these tumors, at least as performed by the average surgeon, often results in tumor spillage, resulting in the rapid development of carcinomatosis.[10,16] The retrospective nature of this study limits our ability to completely assess technical issues related to the individual operations performed in SO patients, and we could not assess margin status in every case. However, the proportions of outside patients who had incomplete resections and involved margins were higher, and the proportion of outside patients who had multiorgan resection was lower, compared with the index group. These findings suggest that surgeries performed in the outside patients were in some cases technically incomplete. Surgeons operating on patients with known or suspected ACC should be aware that incomplete resection or tumor spillage at the time of operation virtually guarantees that the patient will develop recurrent disease.

After median follow-up of 7.3 years, patients who had undergone primary surgery at the index institution had a superior DFS and OS to those who had outside surgery, with absolute disease-free and overall survival rates in the index group of 50% and 68%, respectively. We recognize that referral bias accounts in part for the relatively poor outcome of the outside patient population (some were referred to the index institution only after disease recurrence). However, the relative similarity in disease severity as summarized in Table 1 argues in favor of the legitimacy of the comparison of these two groups. Even more importantly, the recurrence rate of the index group (50%) in the current series, the overwhelming majority of whom did not receive adjuvant mitotane, is indistinguishable from that reported for the group that received adjuvant mitotane (49%) in the recent nonrandomized interinstitutional analysis from Europe.[7] In addition, the recurrence rate of the outside group (86%) in the current series is similar to that of the control groups (73% and 91%) in the European series. Study size (218 versus 177 patients) and follow-up intervals (median 88 versus 43.0–67.6 months) in the current study compare very favorably with those of the European series. These results taken together emphasize the importance of completeness of initial surgery in the management of patients with ACC, and suggest that at least part of the differences in the outcomes between the groups reported in the European series were related to quality and completeness of surgery rather than treatment with adjuvant mitotane.

We acknowledge that treatment with mitotane has an important role in the management of patients with ACC. In the current retrospective analysis, the groups that did or did not receive adjuvant mitotane were relatively well balanced with regard to disease severity at presentation; we cannot exclude the possibility of a slight bias on the part of physicians to use mitotane in patients who had undergone laparoscopic resection, had an advanced stage of disease, or had histologically involved margins (a potential bias *against* those who received adjuvant mitotane). Despite this relative balance, patients who received adjuvant mitotane had improved DFS compared with those who did not receive mitotane (median DFS 30 versus 12 months, $P = 0.05$); we were unable to detect an OS benefit for adjuvant mitotane. While the majority of patients in this series who received adjuvant mitotane were in the outside group, the benefit of mitotane was not necessarily limited to this population, since when we removed the index patients from the adjuvant mitotane analysis the association of adjuvant mitotane therapy with improved DFS weakened. When we compared the outcome of patients treated with adjuvant mitotane to those treated according to the alternative strategy of withholding mitotane until after recurrence developed, we found no significant difference in OS between these two groups; however, the trend favored the strategy of adjuvant mitotane following initial surgery (median OS 30 versus 14 months, $P = 0.16$). Finally, since there has not been universal agreement on timing of initiation of adjuvant mitotane therapy, and since the European group did not provide such a definition in their manuscript, while we used 6 months from date of surgery as the cutoff for adjuvant mitotane therapy, we also conducted a sensitivity analysis to examine the impact of an earlier cutoff of 2 months on outcome. The more restrictive 2-month cutoff significantly weakened the association of adjuvant mitotane with DFS; this suggests that either sample size or selection bias may have an impact on the association of adjuvant mitotane with recurrence in patients with ACC. Additional investigation will be required to evaluate whether the dose administered, or the level achieved, is an important predictor of outcome in patients who receive mitotane in the adjuvant setting.

Taken together, these results suggest that adjuvant mitotane might at least delay recurrence following surgery for ACC. Thus our data could be taken as partial support for the findings of the European group, insofar as both

investigations found adjuvant mitotane therapy to be associated with improved DFS, and both failed to document a consistent association of adjuvant mitotane with improved OS. We acknowledge that we cannot exclude the possible contribution of other treatments, including systemic chemotherapy treatments, to the outcome of the patients included in this study. However, we did not include an analysis of chemotherapy in the current study since chemotherapy for patients with ACC (a) has not been demonstrated to prolong survival, (b) has not been standardized, (c) is often delivered as multiple sequential regimens, and (d) is rarely administered in the adjuvant setting.

Based on these observations, we continue to favor individualization of decisions regarding treatment of ACC patients with adjuvant mitotane. Because of the complexity and toxicity of mitotane therapy, adjuvant treatment with mitotane may be particularly attractive in relatively young patients with excellent performance status and limited comorbidity.[17–19] In addition, it may be particularly important to consider adjuvant mitotane if there is evidence for incomplete surgery or a histologically involved margin, or if there was lymph node or distant organ involvement or major venous tumor thrombus. Finally, it is reasonable to consider adjuvant mitotane either before or after resection of recurrent or metastatic ACC (particularly if mitotane has not been administered previously).[8]

In summary, in this analysis of a large series of patients with ACC treated with surgery and evaluated at a single institution, patients who had their initial surgery at the index institution had long-term outcomes that compare favorably with those reported by others for patients treated with the combination of surgery plus adjuvant mitotane. These results emphasize the primary role of high-quality surgery that results in complete resection of all gross disease in the management of patients with ACC. Adjuvant mitotane may delay recurrence following primary surgery for ACC. However, the toxicity of mitotane therapy and the absence of a consistently demonstrated survival benefit continue to argue in favor of an individualized approach to the selection of patients for adjuvant mitotane therapy, at least until an international randomized trial can be completed.

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